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Control of drug crystallization in transdermal matrix system

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Abstract

Supersaturation of a drug in a transdermal system is often desirable in order to deliver a target therapeutic dose into the body. Preventing drug crystallization during storage is of importance for such a metastable system. In this study, the following additives were examined under various conditions for transdermal systems: polyvinylpyrrolidone (PVP) and its derivatives; dextrin derivatives; polyethylene glycol (PEG); polypropylene glycol (PPG); mannitol; and glycerin. Norethindrone acetate (NETA) was used as the model drug. The effects of several variables, such as storage temperature and drug loading, on crystallization were also investigated. PVP was found to be the most effective crystallization inhibitor. A lower storage temperature, i.e. 4°C, could significantly increase the induction time of drug crystallization in monolithic matrix transdermal systems.

Keywords: Crystallization inhibitors; Inhibition of drug crystallization in transdermal system; Steroid drugs; Crystal formation

1. Introduction

In the area of transdermal drug delivery, numerous approaches have been investigated to increase skin permeation, including the use of different type of devices (Kydonieus and Berner, 1987; Chien et al., 1989), incorporation of enhancers (Pershing et al., 1993; Meshulam et al., 1993) or, simply, increased drug loading (Pellett et al., 1994; Bialik et al., 1993). In monolithic transdermal systems, the drug is dissolved or dispersed in a pressure-sensitive adhesive (PSA) matrix. To deliver a desired therapeutic dose into the body, a supersaturated concentration of drug might be preferable to an enhancer. It has been demonstrated that drug permeation increases with drug thermodynamic activity beyond saturation to a supersaturated level (Davis and Hadgraft, 1991).

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However, such systems are thermodynamically unstable and the supersaturated drug has a tendency to form crystals, which may cause a reduction in skin permeation. Therefore, the control of drug crystallization is of particular interest for the efficiency and quality of transdermal systems.

In this study, monomeric and polymeric additives were investigated in monolithic transdermal systems. The critical variables are the inhibitory capacity of the additives, storage temperature, and drug loading in the systems. A gestagen, NETA, was used as the model drug and acrylic adhesive was used as the model adhesive. Different types of additives were evaluated, including PVP and its derivatives, dextrin derivatives, PEG, PPG, mannitol and glycerin.

2. Materials and methods

2.1. Materials

NETA was obtained from Diosynth Corp. Acrylic adhesives were obtained from Monsanto (St. Louis, MO) and National Starch and Chemical (Bridgewater, NJ). Release liners and backing films were obtained from 3M Pharmaceuticals (St. Paul, MN). PVP (MW = 30 000 and 90 000) was obtained from BASF (Parsippany, NJ). PVP–vinyl acetate (PVP/VA s-630 and PVP–hexadecene were ordered from ISP Technologies (Wayne, NJ). Hydroxypropyl cyclodextrin (HPCD), PEG 900, PPG 4000, mannitol and glycerin were purchased from Aldrich Chemical (Milwaukee, WI). Sucrose laurate was purchased from RITA (Crystal Lake, IL).

2.2. Preparation of monolithic transdermal systems

NETA was dissolved in acrylic adhesive solutions. The mixed solutions were rotated until the drug was completely dissolved. Additives were then added (5–10%, w/w). Some additives (mannitol, HPCD and sucrose laurate) could not be dissolved in the adhesive solvent; these were dispersed in the solutions. The drug-containing adhesive mixture was cast on a release liner film using a Gardner knife and then dried in a ventilated oven at 70°C for 30 min. The final dry thickness of the adhesive layer was approximately 100 mm. A transparent backing film was then placed on the drug–adhesive matrix.

2.3. Monitoring crystal formation

The monolithic transdermal systems were put in sealed plastic bags and stored at three different temperatures: 4, 23 and 45°C. Appearance of drug crystals was monitored visually and microscopically (Olympus Microscopes, Tokyo, Japan) throughout the whole area of systems (15×25 cm). The time intervals were specified bi-weekly for the first 3 months and then monthly for up to 10 months. The number of drug crystals after 9 months storage was counted in a region of 25 cm^2 within the larger area (375 cm^2) of the whole system samples.

3. Results and discussion

This study was focused on stabilizing the transdermal systems and identifying the best conditions for preventing drug crystallization during long-term storage. Therefore, the time intervals of monitoring crystallization were rather wide and one large laminate was examined for each condition. The results from this study should be representative and provide qualitative trends rather than quantitative measurement of the factors affecting drug crystallization.

3.1. Effects of additives on induction time

Matrix systems were formulated and compared on a weight basis (w/w). Ten formulations with nine different additives at concentrations from 5 to 10% were examined, including a drug–acrylic adhesive matrix without any additives as a control. Among the nine additives tested, PVP with an MW of 30 000 showed the best crystallization inhibitory ability in the acrylic adhesives (Fig. 1). At 10% drug and 10% PVP level (w/w), no drug crystals were observed microscopically until 9 months storage at 23°C. Drug crystals were ob-

served in the formulation without additives (control) after 3 months storage under the same conditions. After adding two different molecular weight PVPs at the same weight percentage, it was found that the order of inhibition ability for drug crystallization was PVP 30 000 > PVP 90 000. PVP derivatives, however, could not inhibit drug crystallization as effectively as PVP under the same conditions (Fig. 1).

PVP has been used as a drug crystallization inhibitor in pharmaceutical formulations for many years. Using different molecular weights and concentrations of PVP, Simonelli and coworkers reported that the relative diffusivity of PVP and sulfathiazole from bulk solution to crystal surface was crucial for the rate of crystal growth (Simonelli et al., 1970). Ziller and Rupprecht investigated the interactions between drug and PVP in aqueous suspension during temperature cycling (Ziller and Rupprecht, 1988). They suggested that the inhibitory effect of PVP on drug crystallization in aqueous suspension may be primarily attributed to the protective PVP layers

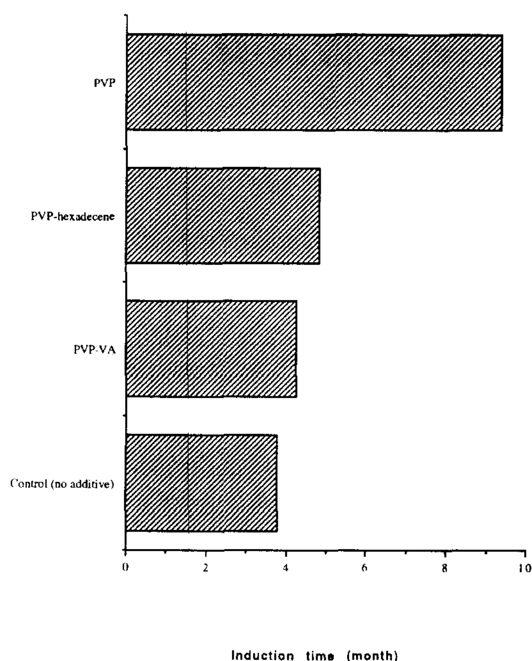

Fig. 1. Effect of additives on inhibition of crystallization at 23°C. Formulation: 10% NETA in acrylic adhesive with 10% additives.

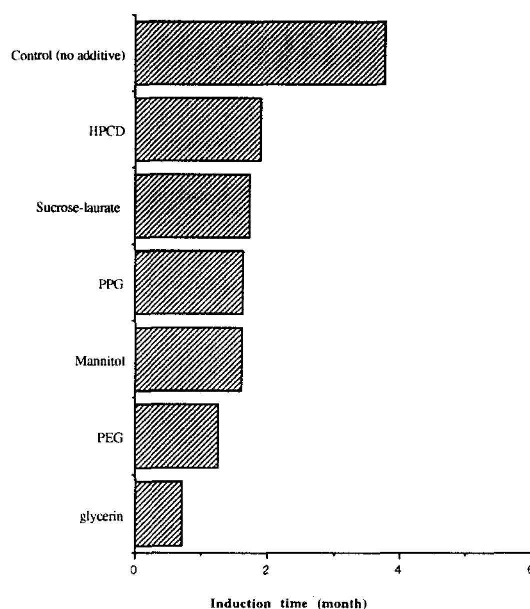

Fig. 2. Effect of additives on acceleration of drug crystallization at 23°C. Formulation: 10% NETA in acrylic adhesive with 10% additives.

adsorbed on the crystal surfaces. In the case of a transdermal matrix system, the polymeric adhesives are considered as solvents of the drug. PVP may interact and adsorb onto the NETA nuclei or initial crystals, and thus prevent drug crystal growth. Since polymeric adhesive matrix systems are more complicated than aqueous solutions, studies need to be conducted to further explore or confirm the inhibition mechanisms.

Drug crystals formed rather quickly in the presence of saccharide and triol-type compounds (Fig. 2). With 5% mannitol, HPCD or glycerin (w/w), drug crystals formed even faster than the control formulation (without additive), suggesting that those additives may accelerate the drug crystal growth in acrylic adhesives. Several surfactants, such as sucrose laurate, PEG and PPG, were also investigated in this study. It appeared that surfactants with balanced hydrophilic and hydrophobic groups did not facilitate the inhibition of drug crystallization (Fig. 2). Although these mechanisms need to be further investigated, this suggested that several factors may play a role in crystal growth acceleration, including the polar

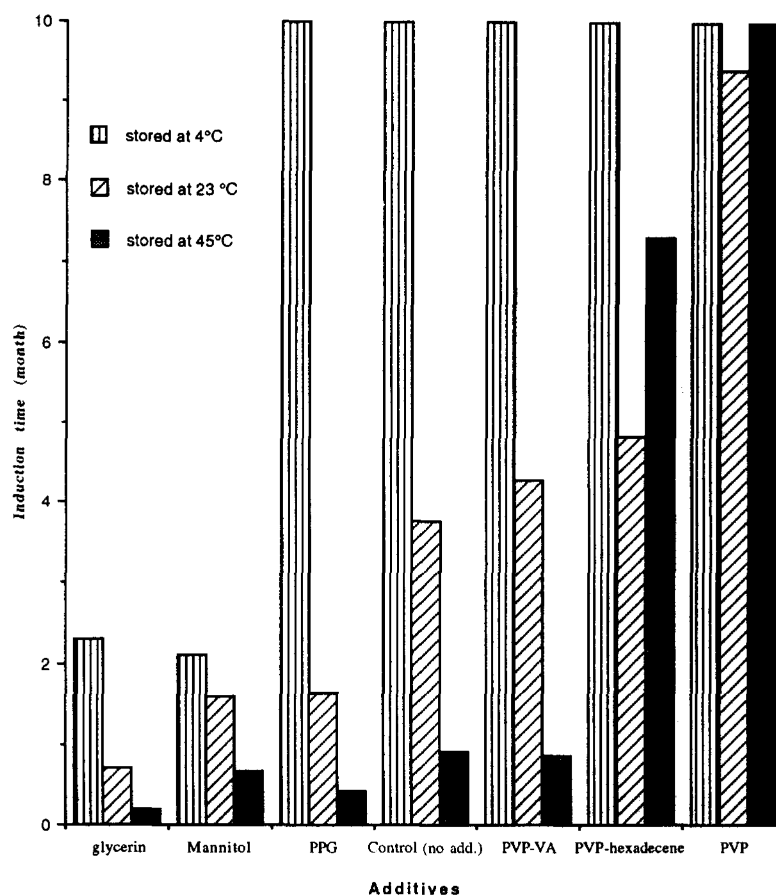

Fig. 3. Effect of temperature on drug crystallization. Formulation: 10% NETA in acrylic adhesive with 10% PVP (MW = 30 000).

nature of those compounds or crystals as seeds due to low solubility of those additives.

3.2. Effects of temperature

It was found that storage temperature has a major impact on the induction time of drug crystallization. Drug crystal formation at different storage temperatures was monitored for up to 10 months. As illustrated in Fig. 3, in most cases, drug crystals were formed faster at 45°C than at 4° or 23°C. However, for PVP and PVP–hexadecene, drug crystallization appeared to be faster at 23°C than at 45°C in this study. The drug crystallized much more slowly at 4°C than at 23°C (Fig. 3). These observations suggest that temperature is one of the crucial factors governing the induction time of steroid drug crystallization in a solid matrix system. However, crystallization in a polymeric matrix is a rather complicated process. Solubility is not the only factor affecting the drug crystallization process. Storage temperatures may affect drug crystallization through several other factors. For example, crystallization is controlled by the diffusion of a drug molecule on to the drug crystals. Diffusion of molecules is dependent on temperature, especially for small molecules from or through the bulk polymeric solid matrix to an impingement site. Rate of crystal growth can also be controlled by a surface integration process. A thorough investigation may shed some light on mechanisms of drug crystallization in the polymeric systems.

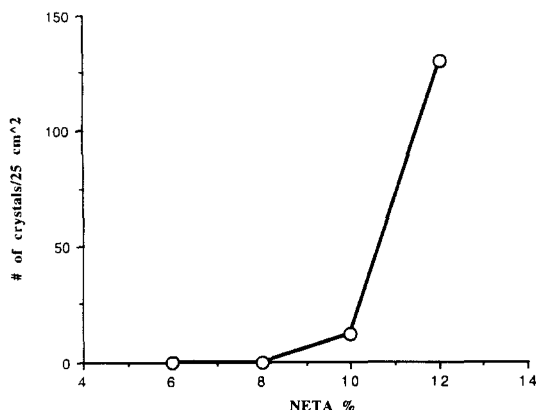

Fig. 4. Effect of drug loading on drug crystallization at 23°C. Formulation: various loading of NETA in acrylic adhesive with 10% PVP (MW = 30 000).

3.3. *Effects of drug loading*

Drug loading from 4 to 12% of the total solid (w/w) was evaluated in the acrylic adhesives. With 12% of drug in the matrices, drug crystals were observed within 1 month at 23°C, even in the presence of 10% PVP. As shown in Fig. 4, the number of NETA crystals was increased approximately 15-fold as the NETA loading increased 1.2-fold from 10 to 12%. A higher degree of supersaturation was thermodynamically less stable due to a higher chemical potential of the dissolved form than of the solid phase. Therefore, rates of nucleation and crystal growth increased with drug supersaturation level (Rodriguez-Hornedo et al., 1990).

4. Conclusion

In the present study, additives for transdermal systems were selected and examined. Crystallization of a steroid drug in transdermal systems was monitored under various conditions. The conclusions from this study were that steroid drug crystallization in acrylic adhesives depends on additives, drug concentration and storage temperatures. Crystal formation can be controlled by adjusting these factors. Under these experimental conditions, PVP was found to be the most effective crystallization inhibitor. Lower storage temperature and lower drug loading could also help in increase of the induction time of drug crystallization in transdermal systems.

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