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Selection and Use of Crystallization Inhibitors for Matrix-type Transdermal Drug-delivery Systems Containing Sex Steroids*

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Abstract

The purpose of this study was to stabilize transdermal drug-delivery systems (TDDS) highly loaded with sex steroids against recrystallization of drugs during storage. To facilitate the selection of potential crystallization inhibitors a drug–excipient interaction test was also established.

Analysis of the thermal behaviour of 1 : 1 steroid–excipient mixtures by differential scanning calorimetry (DSC) revealed that oestradiol and gestodene interact strongly with silicone dioxide and povidones, e.g. povidone K12. The addition of povidone K12 to polyacrylate-based matrix TDDS containing either 3% oestradiol or 2% gestodene resulted in stable systems which did not recrystallize during storage at 25°C for more than 5 years. Significant recrystallization was, on the other hand, observed in non-stabilized reference patches even after 1 to 2 months storage.

The DSC screening model proved very effective for selection of inhibitors of the crystallization of sex steroids in matrix TDDS. The crystallization inhibitor approach is a highly versatile stabilization tool for matrix patches containing high concentrations of sex steroids.

The rate of percutaneous drug absorption from matrix-type TDDS is to some extent dependent on the concentration gradient between the delivery system and the skin, as described previously for testosterone and oestradiol (Yu et al 1991). Therefore, TDDS containing high concentrations of drug generally promote high drug fluxes and lead to high daily steroid dosages from relatively small, and thus attractive, systems. For several sex steroids however, the saturation solubility in standard pressure-sensitive adhesives is low. As a consequence, drug substance which is readily dissolved during the process of manufacturing of the patch and also immediately thereafter, might partially recrystallize during storage of the systems (Yu et al 1991). Two examples of drug recrystallization from TDDS containing either 3% of the natural oestrogen 17β-oestradiol or 2% gestodene are shown in Figure 1.

A previous study demonstrated that oestradiol recrystallizes in the form of its hemihydrate from polyacrylate-based TDDS whereas gestodene recrystallizes in its anhydrous polymorphic form I (Lipp & Müller-Fahrnow 1994). Such physical instability might lead to reduced drug fluxes from affected patches after a longer period of storage. Several approaches can be used to prevent drug recrystallization. Although one possibility is to reduce the drug load of the system, the formation of crystals during storage has been reported for TDDS containing oestradiol concentrations as low as 2% (Yu et al 1991) or 1·5% (Stefano et al 1997). A further reduction of the oestradiol load is unattractive because the patch size would need to be increased to maintain a sufficiently high daily drug absorption from the resulting TDDS. One basic approach to enhancing the solubility of the drug in the patch formulation is prodrug formation (Lipp et al 1995); other options for increasing the drug loading level in patches are adhesive modification (Carring & Therriault 1997), use of co-solvents (Barry 1983), and the use of crystallization inhibitors within supersaturated TDDS (Lipp et al 1993; Ma et al 1996).

The application of crystallization inhibitors within supersaturated solutions of drugs in water and organic solvents, or mixtures of both, has been the topic of several recent studies (Yeoh 1994; Hendriksen & Grant 1995; Kubota et al 1997), and

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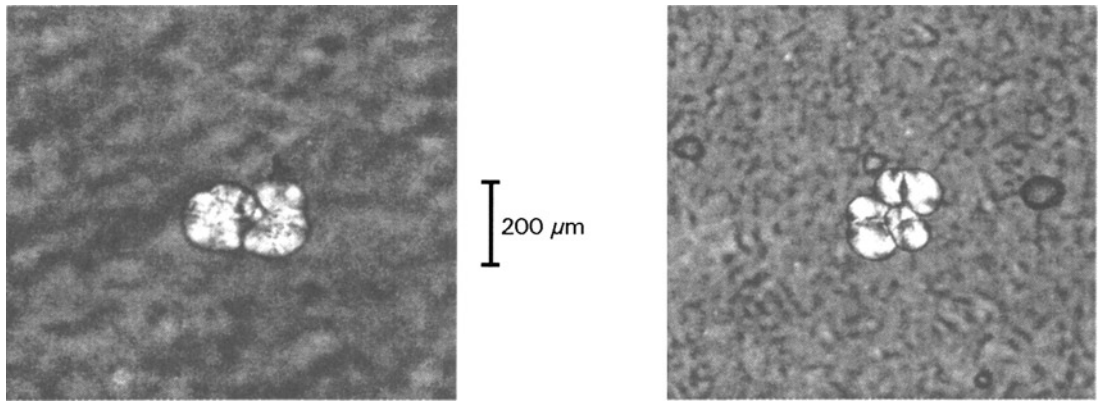

Figure 1. Drug crystals in polyacrylate-based transdermal drug-delivery systems (TDDS) containing 3% oestradiol (A) or 2% gestodene (B). The pictures were taken after 3 months storage at 25°C. Immediately after manufacture the TDDS were free from drug crystals.

the transdermal penetration of drugs from supersaturated solutions has also been investigated (Pellet et al 1997).

The primary goal of the current work was to select potent inhibitors of the crystallization of oestradiol and gestodene (Figure 2) to enhance the loading level of the drugs in polyacrylate-based matrix TDDS without the risk of formation of drug crystals during storage. Furthermore, the often time-consuming work involved in formulation optimization should be minimized by establishing a time-saving screening model for the efficient selection of crystallization inhibitors.

Materials and Methods

Materials

Oestradiol, as its hemihydrate, and gestodene (both drug grade; Schering, Berlin, Germany) were both used in the micronized form. The materials used within the DSC screening process were: cholesterol (Merck, Darmstadt, Germany), colloidal anhydrous silica (Aerosil 200, Aerosil 380; Degussa, Frankfurt, Germany), copovidone, crospovidone (both from BASF, Ludwigshafen, Germany), hydrophobic silica (Aerosil R812, Aerosil R972; Degussa), hydroxypropyl-β-cyclodextrin (Wacker Chemie, München, Germany), hydroxy-ethylcellulose (Cellosize WP-300; Nordmann–Rassmann, Hamburg, Germany; Tylose H 30 000 YP, Hoechst, Frankfurt, Germany), imidazolyl urea (Merck), poly(acrylic acid) (Carbopol 950, BF Goodrich, Cleveland, OH), povidone (povidone K12, K17 K25, K30; BASF), silica gel (various types, Table 1, all from Merck), and sodium alginate (Fluka, Germany).

Differential scanning calorimetry

Binary mixtures of steroid and excipient were produced by weighing the materials into the steel chamber of a vibration mill and mixing for 5 min. The resulting physical mixtures were subjected to differential scanning calorimetry (DSC) using Mettler instruments (TA 3000 or TA 4000; Mettler–Toledo, Gießen, Germany). A temperature program starting at 30°C was run with a slope of 10° min^{-1}. The end-points were 210°C for mixtures containing oestradiol hemihydrate and 230°C for mixtures containing gestodene. For reference

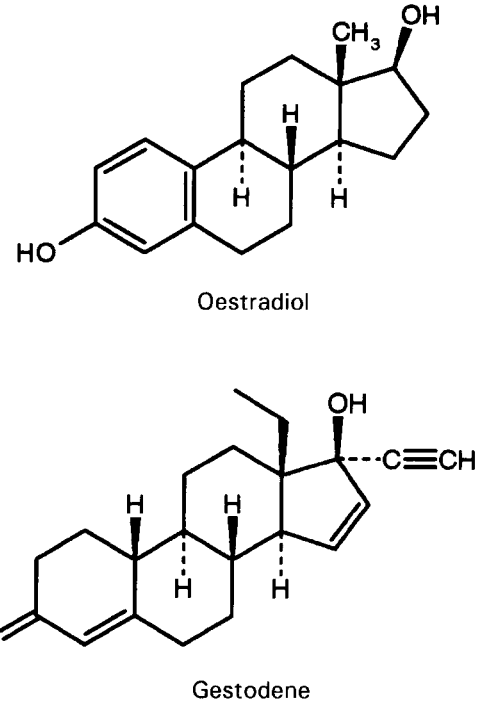

Figure 2. The structural formulae of oestradiol and gestodene.

purposes pure steroids were subjected to the same procedure.

TDDS production

Patches were produced in a discontinuous manner by means of an Erichsen coater (Hemer–Sandwig, Germany) model 335/I. The steroids were dissolved with the povidones in sufficient 2-propanol and these mixtures were added to Gelva 788 polyacrylic pressure-sensitive adhesive (50% solids in ethyl acetate; Solutia, Springfield, MA). The resulting wet mix was coated onto silicone-treated polyester (Bertek, St Albans, VT) by means of a 300-μm knife. After oven drying for 20 min at 70°C lamination was performed with Saran/Hytrel-coextrudate (Bertek). The three-layered sheets obtained were used to die-cut circular TDDS of 10 cm^2 area. Initial microscopic examination was performed directly after manufacturing and the remaining TDDS were packaged into composite foil bags which were heat-sealed and stored at 25°C and 40°C for stability testing.

Polarized-light microscopy

The search for crystals within the patch matrices was performed with a Leitz (Bensheim, Germany) Laborlux S. Patches (10 cm^2) were removed from the release liner and applied to an object slide. Linear polarization equipment combined with a λ-plate was applied to distinguish crystalline structures from the amorphous patch matrix. Three patches were checked for each set of storage conditions at each time-point. Measurement of crystal dimensions and photo documentation was performed with the Leitz Quantimet 500 PC system.

Results

Several pharmaceutically acceptable excipients were selected for DSC screening of drug–excipient interactions. Physical mixtures of equal amounts of the excipients and micronized 17β-oestradiol hemihydrate were produced in a vibration mill and their thermal behaviour was studied by DSC. The results of these investigations and reference data from the pure steroid are given in Table 1. In a reference experiment the influence of 5 min milling on the thermal behaviour of pure micronized oestradiol hemihydrate was checked and proved to be of no relevance. The heat of fusion of micronized oestradiol hemihydrate was 103·9 $J g^{-1}$ before milling and 101·3 $J g^{-1}$ after. The melting points were 177·7°C before milling and 178·3°C after.

Whereas the melting point of oestradiol in its binary drug–excipient mixtures was not usually much affected, in several cases the heat of fusion was substantially affected. This was especially true for mixtures of oestradiol with povidone (povidone K30) and with colloidal anhydrous silica (Aerosil 200) and these were chosen for further investigation. As the next step a series of binary mixtures of oestradiol and colloidal anhydrous silica (Aerosil 200) with excipient-to-drug ratios from 0·1 to 1·3 were produced and subjected to the same DSC program as previously used for the pure drug and the 1 : 1 mixture. The measurements were performed in triplicate and the relative standard deviation of the heat of fusion was always below 6·5%. The heat of fusion/unit mass of drug decreased linearly with excipient-to-drug ratio

Table 1. Thermal behaviour of oestradiol hemihydrate and its binary 1 : 1 mixtures with different excipients.

Specimen	Heat of fusion ($J g^{-1}$ drug)	Melting point (°C)
Oestradiol	103·9	177·7
Oestradiol + cholesterol	60·5	140·5
Oestradiol + colloidal anhydrous silica (Aerosil 200)	24·8	175·2
Oestradiol + hydroxyethylcellulose (Cellosize WP-300)	66·4	178·0
Oestradiol + hydroxyethylcellulose (Tylose H 30 000)	58·9	173·2
Oestradiol + hydroxypropyl-β-cyclodextrin	75·1	169·6
Oestradiol + imidazolyl urea	97·1	179·0
Oestradiol + polyacrylic acid	94·1	178·2
Oestradiol + povidone K30	12·1	159·2
Oestradiol + sodium alginate	84·7	179·9

Oestradiol was in the form of its hemihydrate.

Table 2. Thermal behaviour of binary 1 : 1 mixtures of oestradiol hemihydrate with several types of silica, silica gel and povidone.

Excipient	Heat of fusion ($J g^{-1}$ drug)	Melting point (°C)
Colloidal anhydrous silica (Aerosil 200)	24·8	175·2
Colloidal anhydrous silica (Aerosil 380)	43·2	174·1
Hydrophobic silica (Aerosil R812)	77·0	175·7
Hydrophobic silica (Aerosil R972)	89·2	175·9
Silica gel 40, 0·063–0·2 mm	35·0	177·3
Silica gel 60, 0·015–0·04 mm	14·8	176·3
Silica gel 60, 0·04–0·063 mm	14·8	176·3
Silica gel 60, 0·063–0·2 mm	8·9	176·5
Silica gel 100, 0·063–0·2 mm	12·9	173·5
Povidone K12	–*	–*
Povidone K17	–*	–*
Povidone K25	13·2	160·1
Povidone K30	12·1	159·2
Crospovidone	10·3	167·5
Copovidone	–*	–*

* No fusion or melting point detectable.

(Figure 3). Linear regression of the data obtained resulted in the equation:

$$y = 102{\cdot}2 - 78{\cdot}7x \quad (1)$$

where y denotes the heat of fusion of oestradiol ($J\,g^{-1}$) and x denotes the ratio of Aerosil 200 to oestradiol. The function has a correlation coefficient of $r = 0{\cdot}997$.

Because the data obtained within the first screening series (Table 1) had drawn attention to two classes of excipient, silicon dioxide and povidones, in a second screening series several members of these two classes were investigated. The results of these investigations are given in Table 2.

Again it was apparent that among the binary mixtures tested the influence on the heat of fusion was greater than that on melting point. Of the silica excipients, hydrophilic samples such as Aerosil 200 and Aerosil 380 and silica gels 40, 60, and 100 had significant impacts on the heat of fusion whereas the hydrophobically substituted silicas Aerosil R 812 and R 972 did not. Among the povidones it was apparent that the linear homopolymers, especially those of lower molecular weight, e.g. povidone K12, had a more pronounced influence on the melting behaviour than those of higher molecular weight, e.g. povidone K30. The cross-linked homopolymer (crospovidone) and the linear heterocopolymer with vinyl acetate (copovidone) also had a significant influence on the melting behaviour of oestradiol. In essence a very strong drug–excipient interaction was measured for the povidones, especially povidones K12, K17 and copovidone. No oestradiol phase transition could be detected during DSC experiments with 1 : 1 mixtures of drug and these excipients.

Colloidal anhydrous silica (Aerosil 200), povidone K12, and copovidone, excipients with a pronounced influence on the melting behaviour of oestradiol, were selected for investigation of their influence on the melting behaviour of gestodene. Results from DSC investigations of 1 : 1 mixtures of gestodene with these excipients are given in Table 3. The influence of colloidal anhydrous silica on the melting behaviour of the steroid gestodene is illustrated in Figure 4.

Although colloidal anhydrous silica (Aerosil 200), povidone K12 and copovidone had a significant influence on the heat of fusion of gestodene in the binary mixtures, the drug–excipient interaction was distinctly lower than the interaction with oestradiol. The peak corresponding to melting of gestodene could always be detected. The greatest reduction of the heat of fusion of gestodene, to $28{\cdot}6\,J\,g^{-1}$, was obtained for the mixture with povidone K12.

Because povidone K12 had a significant influence on the melting behaviour of the two steroids gestodene and oestradiol this excipient was chosen for formulation experiments. The second part of the study was to check whether povidone K12 inhibited the formation of drug crystals within matrix patches. TDDS were produced from matrices comprising either 2% gestodene or 3% oestradiol plus different amounts of povidone K12 (between 0 and 16% for oestradiol and between 0 and 20% for gestodene). The TDDS matrix was always made up to 100% with polyacrylic pressure-sensitive adhesive. Immediately after manufacture all TDDS

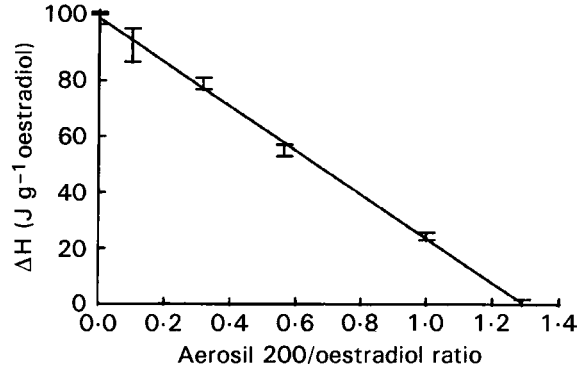

Figure 3. Influence of the drug-to-excipient ratio on the heat of fusion of oestradiol hemihydrate.

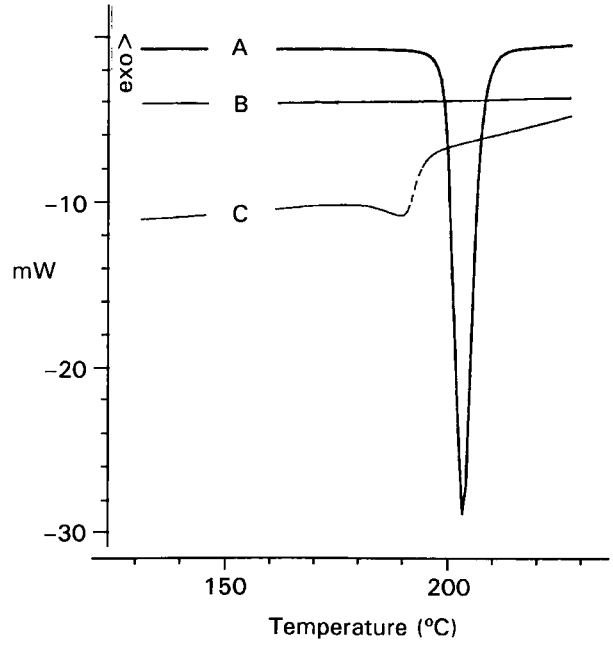

Figure 4. Differential-scanning calorimetry curves for gestodene (A), colloidal anhydrous silica (B), and their 1 : 1 mixture (C).

Table 3. Thermal behaviour of gestodene and its binary 1 : 1-mixtures with several excipients.

Specimen	Heat of fusion ($J g^{-1}$ drug)	Melting point (°C)
Gestodene	112·1	200·4
Gestodene + colloidal anhydrous silica (Aerosil 200)	30·3	190·1
Gestodene + copovidone	36·2	178·9
Gestodene + povidone K12	28·6	166·0

were shown by examination with polarized-light microscopy to be free from drug crystals. Drug recrystallization was followed by microscopic examination of patches stored at 25°C and 40°C. For each time-point and set of storage conditions three 10-cm^2 patches were examined by scanning the whole TDDS area. The results of these examinations, i.e. the numbers of TDDS containing drug crystals, are summarized in Tables 4 and 5.

Crystal growth was detectable within two months of production in gestodene-containing reference patches produced without povidone K12. The same was true for patches containing 5% excipient. The addition of 10% or 15% povidone K12 fully stabilized the resulting formulations over a time-period of 5 months; gestodene crystals were apparent after 14 months storage in several TDDS containing 10 or 15% excipient. The addition of 20% excipient resulted in patches stable for 63 months at 25°C.

In oestradiol-containing patches drug recrystallization started rapidly, i.e. after 1 month, in povidone-free reference samples only. Although at least 8% povidone K12 was needed to keep the TDDS free from drug crystals for 12 months at 40°C, addition of 2% excipient was sufficient to stabilize the oestradiol TDDS against drug recrystallization for up to 62 months at 25°C.

The significant effect of povidone K12 in oestradiol patches was especially evident from comparison of photomicrographs of stabilized and non-stabilized formulations after 12 months storage at 25°C (Figure 5a, b). Whereas many drug crystals were apparent in the excipient-free patch (a), the

Table 4. Recrystallization of oestradiol during storage of matrix transdermal drug-delivery systems containing different concentrations of povidone K12.

Concentration of povidone K12 (%)	Storage time and conditions						
	1 Month		3 Months		12 Months		62 Months
	25°C	40°C	25°C	40°C	25°C	40°C	25°C
0	3	3	3	3	3	3	3
2	0	0	0	0	0	2	0
4	0	0	0	0	0	1	0
8	0	0	n.d.	n.d.	0	0	0
12	0	0	n.d.	n.d.	0	0	0
16	0	0	n.d.	n.d.	0	0	0

n.d. = not determined. The values are the number of transdermal drug-delivery systems (out of 3) containing drug crystals.

Table 5. Recrystallization of gestodene during storage of matrix transdermal drug-delivery systems containing different concentrations of povidone K12.

Concentration of povidone K12 (%)	Storage time and conditions								
	1 Month		2 Months		5 Months		14 Months		63 Months
	25°C	40°C	25°C	40°C	25°C	40°C	25°C	40°C	25°C
0	0	0	3	3	3	3	3	3	3
5	0	0	3	3	3	3	3	3	3
10	0	0	0	0	0	0	1	1	0
15	0	0	0	0	n.d.	n.d.	2	1	0
20	0	0	0	0	n.d.	n.d.	0	0	0

n.d. = not determined. The values are the number of transdermal drug-delivery systems (out of 3) containing drug crystals.

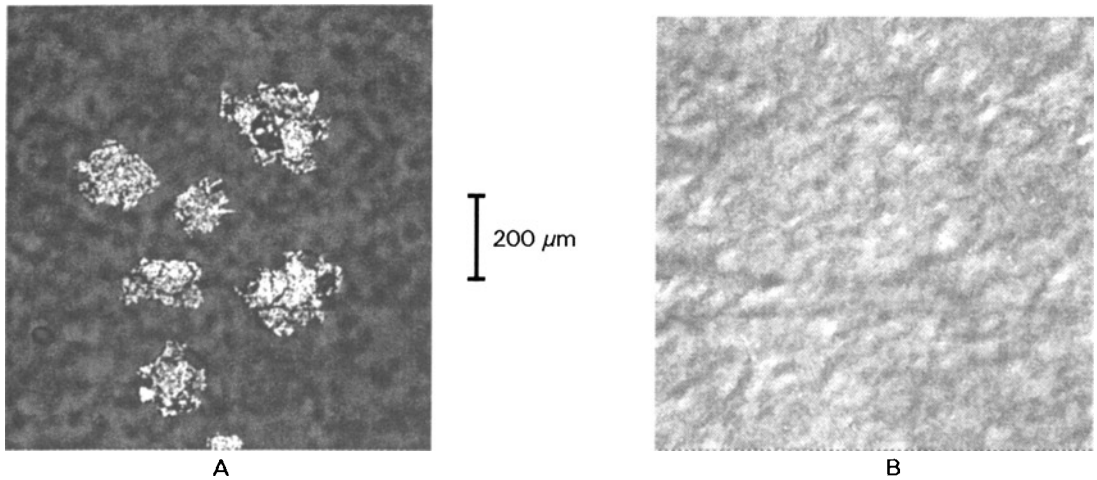

Figure 5. Photomicrograph of matrix transdermal drug-delivery system containing oestradiol after storage for 12 months: (a) reference patch without povidone; (b) stabilized patch containing 8% povidone K12.

stabilized patch containing 8% povidone K12 (b) was completely free from crystals.

Discussion

During the routine production of matrix TDDS from polyacrylate pressure-sensitive adhesive by the solvent cast process, dissolution of the steroid in a solution of the adhesive in organic solvent(s) is an essential step. After addition of excipients such as penetration enhancers the resulting wet mix is normally coated on to a release liner and the organic solvent (mixture) is rapidly removed in either a continuous or discontinuous process. This procedure leads to supersaturated systems if the saturation solubility of the drug in the resulting TDDS matrix is lower than its actual loading level. However, because of the high viscosities of the resulting systems and, especially, the relatively low diffusion coefficients of the steroids in matrix TDDS (approx. $1 \times 10^{-9}\,cm^2\,s^{-1}$; Hartisch 1994) recrystallization of the drug substance might not occur very rapidly. Thus crystals were not apparent immediately after manufacture in the oestradiol- and gestodene-containing patches prepared in this study. However, after only 1 or 2 months storage drug crystals could be detected in several types of TDDS. The first stage of crystallization within supersaturated solutions is the formation of a so-called embryo or subnucleus by collision of single molecules (Roy 1992). If further molecules are attracted to this embryo it might exceed its critical radius and thus will not redissolve in the surrounding solution, i.e. the TDDS matrix, but might attract further molecules and crystal formation will take place. Subsequently, the crystals obtained will grow until the system reaches the state of saturation. Later, as a result of the tendency to reduce the total energy of the system, large crystals might grow larger while small crystals might redissolve. For supersaturated steroid-containing patches the following equilibria are, therefore, of primary interest:

$$\text{steroid} + \text{n steroids} \rightleftharpoons \text{embryo} \quad (1)$$

$$\text{embryo} + \text{n steroids} \rightleftharpoons \text{nucleus} \quad (2)$$

$$\text{nucleus} + \text{n steroids} \rightleftharpoons \text{crystal} \quad (3)$$

$$\text{crystal} + \text{n steroids} \rightleftharpoons \text{larger crystal} \quad (4)$$

Whereas the crystal-growth inhibitors normally used in suspensions are effective within equilibria 3 and 4, crystallization inhibitors influence the first two equilibria in that they will be driven to the side of the educts, i.e. crystallization inhibitors should interact directly with the dissolved steroid molecules themselves rather than protecting already existing crystal surfaces from collision with further drug molecules. Hence, they should interfere directly with the drug on molecular level in the sense of the hypothetical equilibrium 1a:

$$\text{steroid} + \text{crystallization inhibitor} \rightleftharpoons \text{steroid crystallization inhibitor complex} \quad (1a)$$

thereby preventing the formation of the nuclei. Hence, any formation of drug crystals which would subsequently grow in the supersaturated environment could be eliminated.

On the basis of the hypothesis that direct interaction between drug molecule and crystallization inhibitor molecule is required (equilibrium 1a) for efficient prevention of recrystallization, it is apparent that a screening model for crystallization

inhibitors should be capable of detecting this kind of drug–excipient interaction. Therefore, the thermal behaviour of binary mixtures consisting of drug and potential crystallization inhibitor only, was tested for its usefulness as a screening model for drug–excipient interaction.

Whereas significant interaction with the steroids was not apparent for most of the excipients tested in the DSC-screening model, some, e.g. povidone K12, did result in strong interaction. Because no heat of fusion of oestradiol was detectable in the 1:1 excipient–drug mixture, povidone K12 was chosen for formulation experiments in which it was also found to be favourably miscible with polyacrylate adhesive. It also had the desired property of pronounced inhibition of crystal formation, stabilizing patches containing either 3% oestradiol or 2% gestodene for more than 5 years against drug recrystallization.

In conclusion, the DSC-screening model proved useful and time-saving for selection of crystallization inhibitors. Povidones and different types of silica interact strongly with steroids in this model. Furthermore, povidone K12 inhibited the crystallization of oestradiol and gestodene in polyacrylate matrices. Thus stable matrices containing either of the steroids are now available. Hence, the construction of small, and thus attractive, patches for hormone-replacement therapy and for fertility control seems feasible.

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