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Research paper

Influence of adsorbents in transdermal matrix patches on the release and the physical state of ethinyl estradiol and levonorgestrel

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ABSTRACT

The drug release from medium molecular weight polyisobutene patches containing adsorbates (drug content: 0.2% ethinyl estradiol, 1.0% levonorgestrel; adsorbent content: 20%, w/w) increased in the order of no adsorbent < titanium dioxide < MCC < crospovidone. This was attributed to differences in drug crystallinity which increased in the order of crospovidone (crystal free) < MCC < titanium dioxide < no adsorbent and the water uptake which increased in the order of no adsorbent (0.1%) = titanium dioxide (0.1%) < MCC (1.6%) < crospovidone (4.8%) at 90% rh. Patches containing adsorbates onto crospovidone were investigated in detail. Increasing the adsorbate's drug loading increased the drug release up to a crospovidone content of 15% (w/w). Patches were crystal free for crospovidone contents $\geqslant$10% (w/w), which corresponds to a drug loading of crospovidone of 12% (w/w). In conclusion, the incorporation of drug adsorbates onto crospovidone into patches based on polyisobutene significantly increased the drug release (approximately 9.1 times for ethinyl estradiol and 15.4 times for levonorgestrel) and prevented drug recrystallization.

1. Introduction

The transdermal route is not used more widely because it is difficult to get sufficient amounts of drug across the skin. Physical methods (e.g. the use of microneedles), electrically assisted methods (e.g. iontophoresis) and the use of chemical penetration enhancers have been investigated to tackle this problem. But the inherent problem of these strategies is that they have the goal to compromise the stratum corneum's barrier function. This renders them potentially harmful since besides enhancing the drug delivery, they could also facilitate the ingress of foreign substances and microbes.

One alternative approach is the use of supersaturated systems. These systems can easily be manufactured, e.g. by fast solvent evaporation or by dilution of a saturated drug solution in a good solvent with a non-solvent ("mixed cosolvent method"). The drug's increased thermodynamic activity in these formulations led to enhanced drug flux across artificial membranes [1–3], pig skin [4] and human skin [5]. But the supersaturated state is metastable by definition and for thermodynamic reasons drug recrystallization will occur eventually [6]. Since, according to Fick's law of diffusion, only the amount of dissolved drug contributes to the drug flux across the skin, drug recrystallization in transdermal patches may lead to reduced drug delivery [7] and consequently to potentially ineffective drug plasma levels. It is therefore a necessity to prevent drug recrystallization in these formulations for the duration of the shelf-life.

The main factors that prevent drug recrystallization in matrices are thought to be the viscosity of the formulation and interactions between excipient and drug. The latter results in the adsorption of the excipient onto the growing crystal surface. By this means, the crystallization is "poisoned" [8–10]. Additionally, according to a model developed by Raghavan et al., polymer molecules that were rejected at the crystal face can accumulate in the hydrodynamic layer which surrounds it and thereby increase the resistance for the drug diffusion to the crystal [11]. Linear PVP has been used extensively to prevent drugs from recrystallization in solid solutions [10] and in transdermal patches [12–14]. Hydrogen bonds between the amide carbonyl group of the polymer and a hydrogen donor moiety of the drug molecules are probably the predominant reason for the stabilizing effect [9,10], and the optimal polymer concentration was 10% (w/w) [2]. Substituted cellulose-polymers (e.g. HPMC, HPC and MC) have several potential binding sites for hydrogen bonds per unit and were found suitable as antinucleating agents in several studies [11,12,14,15]. Highest flux rates were yielded by 4.8-times saturated hydrocortisone acetate solutions stabilized with different amounts of a variety of stabilizing polymers across silicone membranes when they were stabilized

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with HPC or HPMC in concentrations between 0.5% and 1% [2]. Other excipients that were successfully investigated as antinucleating agents include cyclodextrins [16,17], methacrylic polymers like several Eudragits [18,19] and surfactants, like Tween 80 and Labrasol [7]. Para-acetoxy acetanilide, a tailor-made additive, reduced the growth of acetaminophen crystals [20].

Another approach to inhibit drug recrystallization, which is mainly used for oral dosage forms, is the preparation of drug adsorbates onto insoluble carriers. The drug is adsorbed onto the surface or absorbed into the bulk of the carrier material in a molecularly dispersed state. By this means, the drug molecules are immobilized and thus prevented from aggregating and forming nuclei and crystals. Predominantly, these adsorbates are prepared by the "solvent-deposition method" in which the adsorbent is soaked with a concentrated drug solution in a volatile solvent and subsequently dried. Monkhouse and Lach [21] were the first to investigate the properties of drug-silica adsorbates and attributed the improved dissolution behavior to the "minuscular form" in which the drugs were deposited onto the carriers' surface. Subsequent studies [22–25] suggested that specific drug interactions with the silanol groups immobilized the drug molecules which suppressed the drug crystal formation. Adsorbates onto other carriers have been investigated to lesser extent, but reports exist in the literature about the successful use of cellulose [26,27], colloidal magnesium aluminum silicate [28] and crospovidone [29,30].

The incorporation of adsorbates into transdermal matrix patches could be a promising strategy to prevent drug recrystallization therein. Especially for very lipophilic adhesives, like polyisobutenes or silicones, which show incompatibilities with conventional crystallization inhibitors like linear PVP [31], this might be an interesting alternative. Moreover, recrystallization inhibitors that dissolve in the matrix can alter the drug solubility therein which is detrimental for the drug release [2]. Since the investigated adsorbents are not soluble in the matrix, this problem would be circumvented.

The objective of this study was to investigate the suitability of adsorbates containing the steroid hormones ethinyl estradiol and levonorgestrel onto different carriers for the formulation of transdermal matrix patches. Titanium dioxide, microcrystalline cellulose (MCC) and crospovidone (CPVP) were used as carriers because they are able to form hydrogen bonds [27,32,33] which could lead to the inhibition of drug recrystallization and enhanced drug release.

2. Materials and methods

2.1. Materials

Micronized ethinyl estradiol (Pfannenschmidt, Hamburg, Germany), micronized levonorgestrel (Cayman Chemical, Hamburg, Germany), crosslinked polyvinylpyrrolidone (CPVP) (Kollidon® CL-M and Kollidon® CL) (BASF AG, Ludwigshafen, Germany), microcrystalline cellulose (MCC) (Avicel® PH 200) (FMC Biopolymer, Cork, Ireland), titanium dioxide (Caesar & Loretz GmbH, Hilden, Germany), hydrophilic fumed silica (Aerosil) (Aerosil® 200) (Degussa AG, Düsseldorf, Germany), sodium dodecyl sulfate (Texapon®) (Henkel KGaA, Düsseldorf, Germany), ethanol, isopropanol, ethyl acetate, acetone, methylene chloride, hexane, chloroform, acetonitrile (HPLC grade) (Carl Roth GmbH & Co. KG, Karlsruhe, Germany), methanol (HPLC grade) (Merck KGaA, Darmstadt, Germany), medium molecular weight polyisobutene (MM-PIB) (Oppanol® B 12 SFN) (BASF AG, Ludwigshafen, Germany), release liner (Scotchpak™ 1020), backing liner (CoTran™ 9720) (3 M Medica, Borken, Germany) and polyethylene membrane (Solupor® E-9H01A) (DSM Solutech, Heerlen, The Netherlands).

2.2. Drug solubility in solvents

Excess amounts of ethinyl estradiol or levonorgestrel were added to 5 ml solvent (water, 2% aqueous SDS solution, methanol, ethanol, isopropanol, ethyl acetate, acetone, methylene chloride, chloroform and hexane) in glass vials ($n = 3$). The samples were shaken for at least 5 days at 25 ± 2 °C. Two milliliter samples was taken from the saturated solutions and filtered through a 0.5-μm filter (Sartorius AG, Göttingen, Germany) or centrifuged at 13,000 rpm for 30 min (Heraeus Biofuge 13 Haemo, Heraeus Instruments, Osterode, Germany). The drug concentrations were detected after appropriate dilution as described later.

The ethinyl estradiol solubility in ethanol, ethyl acetate and chloroform was estimated by adding increments of 50 mg ethinyl estradiol to 1.0 ml solvent until the drug did not completely dissolve or a concentration of 200 mg/ml was reached.

2.3. Preparation of adsorbates and matrix patches

2.3.1. Preparation of adsorbates

Adsorbates of ethinyl estradiol and levonorgestrel onto CPVP, Aerosil, MCC and titanium dioxide were prepared by the solvent-deposition method. In general, 450 mg carrier was soaked with 589 μl chloroformic drug solution (containing 4.5 mg ethinyl estradiol and 22.5 mg levonorgestrel) in a mortar followed by immediate mixing with a pestle. The adsorbates were dried at 60 °C for 30 min (UT 6060, Heraeus Instruments, Hanau, Germany).

By varying the ethinyl estradiol and the levonorgestrel concentration in the chloroformic drug solution, adsorbates for patches with different drug contents were prepared. By varying the amount of CPVP, adsorbates for patches with different CPVP contents were prepared.

CPVP fractions with different particle sizes were obtained by classifying Kollidon® CL using sieves. Grinding the polymer (Amplitude: 100, 30 min, without cooling) using a ballmill (MM2000, F. Kurt Retsch GmbH and Co. KG, Haan, Germany) and subsequent separation with a gravity classifier (Multiplex® Zigzag Classifier MZR, Hosokawa Alpine AG, Augsburg, Germany) resulted in the finest fraction with CPVP particles in the lower micrometer range. The particle size distributions were analyzed in aqueous dispersions by laser diffraction (Coulter LS 230, Beckmann-Coulter, Krefeld, Germany) using the Fraunhofer theory.

2.3.2. Preparation of matrix patches

The adhesive solution was prepared by adding small pieces of MM-PIB to chloroform (22.5% w/w) in a glass jar. The mixture was magnetically stirred for 48 h until the MM-PIB pieces were completely dissolved. Its solid content was confirmed by driving off the solvent from a small sample of known weight. In general, 450 mg freshly prepared adsorbate or 589 μl chloroformic drug solution (for patches without adsorbents) was added to a certain amount of MM-PIB solution in a 20-ml glass vessel to yield matrices with 0.2% ethinyl estradiol, 1.0% levonorgestrel, 20% adsorbent and 78.8% MM-PIB after drying. In patches with less than 20% adsorbent, the amount of MM-PIB solution was varied to keep the drug content constant (Table 1). The vessels were closed tightly and the mixtures were magnetically stirred for 4 h until they were homogeneous. One drop of each casting mixture was applied onto a microscopic slide and the absence of drug crystals was confirmed by polarized light microscopy. The casting mixtures were degassed for 30 min in a sonication bath (Retsch GmbH & Co. KG, Haan, Germany) and cast onto the fluorocoated side of the release liner (theoretical film thickness: 500–1500 μm) with a casting knife setup (ZUA 200, MTV Messtechnik, Köln, Germany). The matrices were dried under a hood for 12 h at 25 ± 2 °C and subsequently for 1 h at 60 °C (UT 6060, Heraeus Instruments, Hanau, Germany). After

Table 1
Composition of the investigated matrix patches in%, w,w.

Name	Drug (%)		Adsorbate (%)	MM-PIB (%)
	Ethinyl estradiol	Levonorgestrel		
Without adsorbates	0.2	1.0	0.0	98.8
	0.2	0.0	0.0	99.8
	0.0	1.0	0.0	99.0
Different adsorbates	0.2	1.0	Titanium dioxide: 20.0	78.8
	0.2	1.0	MCC: 20.0	78.8
	0.2	1.0	CPVP: 20.0	78.8
Different drug loadings	0.2	1.0	CPVP: 20.0	78.8
	0.6	0.6	CPVP: 20.0	78.8
	1.0	0.2	CPVP: 20.0	78.8
Different CPVP amounts	0.2	1.0	CPVP: 5.0	93.8
	0.2	1.0	CPVP: 15.0	88.8
	0.2	1.0	CPVP: 20.0	83.8
Different particle size	0.2	1.0	CPVP: 20.0	78.8

cooling to room temperature, the matrices were laminated with the backing liner using a rubber roller. Circular patches (diameter 1.3 cm) for the drug release studies were manually die-cut using a punch.

2.4. Investigation of the drug physical state

2.4.1. Polarized light microscopy

The adsorbates, the casting mixtures and the freshly manufactured patches were investigated with regard to the existence of drug crystals using a polarized light microscope (Axiotrop, Carl Zeiss Jena GmbH, Jena, Germany) connected to a digital camera. The whole surface was scanned with transdermal patches. The images were evaluated using the Easy Measure Software (version 1.0.15; INTEQ Informationstechnik GmbH, Berlin, Germany).

Cross-sections of patches were prepared by cutting off a wedge-shaped piece with a sharp pair of scissors. After placing it on a microscopic slide, pictures of the specimen's thin side were taken.

All microscopic experiments were conducted at ambient temperature.

2.4.2. Differential scanning calorimetry (DSC)

DSC studies were performed using a Mettler DSC 821e (Mettler Toledo, Giessen, Germany). Freshly prepared samples (approx. 5 mg) were weighed into 40-μl aluminum crucibles with three pinholes in their lid. DSC scans were recorded at a heating rate of 15 °C/min from 25 to 250 °C. All experiments were conducted under a nitrogen atmosphere. The melting transitions (T_m) were derived from the computed extrapolated peak maximum, and the enthalpy values (ΔH) were calculated from the area under the transition peaks using the Star® Software version 8.10 (Mettler Toledo, Giessen, Germany). The crystallinity of the drug, *x*% in the formulation was calculated as follows:

$$x\% = \frac{HTm_f}{HTm_c} \cdot \frac{10,000}{P} \quad (1)$$

where HTm_c: area under the curve of the crystalline drug; HTm_f: area under the curve of the drug in the formulation; *P*: drug loading of the formulation, %.

Drug precipitates of ethinyl estradiol and levonorgestrel from chloroform were prepared by placing drug solutions in open vessels under the hood until the solvent was evaporated.

2.5. Drug release studies

Drug release studies were performed ($n = 3$) with freshly prepared patches in static Franz cells with a receptor volume of 8.0 ml and a diffusion area of 1.0 cm^2. The receptor compartment contained 2.0% (w/w) aqueous SDS solution at 37.0 °C (corresponding to 32.0 °C at the release interface) and was stirred at 400 rpm with a magnetic stirrer. Circular patches (diameter: 1.3 cm, film thickness: approximately 170 μm) were centrally attached to circular pieces of hydrophilic, microporous polyethylene membrane (Solupor E-9H01A) with a diameter of 1.6 cm. The membranes with the attached patches were mounted between the donor and the receptor compartment of Franz cells employing some vaseline to prevent leaking. Five hundred microliter samples were taken after 1, 2, 4, 8, 24, 30 and 48 h and analyzed for their drug content. After each sampling, the Franz cells were refilled with 500 μl prewarmed medium and turned upside down to let potentially formed air bubbles escape through the sampling port.

2.6. Drug assay

The hormones were quantified by HPLC using a Shimadzu system consisting of a SCL-10AVP system controller, a LC-10 ADVP pump, a M10 AVP diode array detector, a SIL-10A autosampler and a DGU-14A degasser. A reversed-phase C18 column (Spherimage-80 ODS2, 5 μm, 125 mm × 4.6 mm, Knauer, Berlin, Germany) was used and the mobile phase consisted of water/methanol/acetonitrile (37/21/42 v/v). The temperature was adjusted to 30 °C and the flowrate to 0.8 ml/min. Twenty-five microliter (ethinyl estradiol concentration >0.4 μg/ml) or 75 μl (ethinyl estradiol concentration <0.4 μg/ml) sample was injected. UV-spectrometric detection was performed at 200 nm (ethinyl estradiol concentration <0.4 μg/ml), 280 nm (ethinyl estradiol concentration >0.4 μg/ml) and 243 nm (levonorgestrel).

Quantification of ethinyl estradiol and levonorgestrel (retention times approximately 7.5 and 10.7 min, respectively) was achieved by using the external standard method and the peak area as quantification criteria.

2.7. Water uptake studies

2.7.1. Water uptake (centrifuge method)

Approximately 200 mg dried (80 °C to constant weight) titanium dioxide, MCC and CPVP were accurately weighed into 2.0-ml Eppendorf cups and 1.0 ml water was added ($n = 3$). The suspensions were vortexed and shaken for 1 h at 25 ± 2 °C using

Table 2
Ethinyl estradiol and levonorgestrel solubility in different solvents.

Solvent	Solubility of levonorgestrel (mg/ml)	Solubility of ethinyl estradiol (mg/ml)
Water	$1.4 \times 10^{-3} \pm 0.7$	$6.0 \times 10^{-3} \pm 2.0$
2.0% SDS	$86.4 \times 10^{-3} \pm 1.9$	$553.5 \times 10^{-3} \pm 23.2$
Methanol	15.1 ± 0.4	n.d.
Ethanol	11.3 ± 0.6	>200[a]
Isopropanol	6.0 ± 0.1	n.d.
Ethyl acetate	10.6 ± 0.2	>200[a]
Acetone	11.7 ± 0.2	n.d.
Methylene chloride	23.6 ± 3.0	n.d.
Chloroform	57.3 ± 2.1	>50[a]
Hexane	0.02[b]	0.008[b]

n.d.: not determined.
[a] Solubility was estimated by adding increments of 50 mg ethinyl estradiol to 1.0 ml the solvent until the drug did not completely dissolve or 200 mg/ml were reached ($n = 1$).
[b] $n = 1$.

a horizontal shaker (HS 501 Digital, IKA-Labortechnik, Staufen, Germany). After centrifugation at 5000 rpm for 3 min (Heraeus Biofuge 13 Haemo, Heraeus Instruments, Osterode, Germany), the excess solvent was decanted/removed with a filter paper. The experiment was repeated with different centrifugation conditions (15 min at 13,000 rpm) and subsequent incubation at 25 ± 2 °C for 12 h. The water uptake U_w was defined as follows:

$$U_w = \frac{(m_{eq} - m_0)}{m_0 \cdot \rho} \quad (2)$$

where U_w is the water uptake, ml/g; m_{eq} the mass of adsorbent after equilibration with water, g; m_0 the initial mass of the dried adsorbate, g; ρ is the density of water at 25 °C, g/ml (=0.997 g/ml).

2.7.2. Dynamic vapor sorption (DVS)

Dynamic vapor sorption experiments were conducted using a DVS-1/1000 (Surface Measurement Systems Limited, Alperton, Middlesex, UK) automated moisture sorption instrument. The data were analyzed with DVSWin analysis suite, version 3.3 standard (Surface Measurement Systems Limited, Alperton, Middlesex, UK).

Approximately 0.33 cm^2 of a dried (60 °C for 2 h, UT 6060, Heraeus Instruments, Hanau, Germany) patch without the release liner was inserted (release side up) into the sample chamber. The DVS method started with a drying step (0% RH for 360 min) followed by 90% RH until equilibration or 4000 min was reached. The recorded weight was corrected for the weight of the backing liner (which showed no significant water uptake) to determine the water uptake of the matrix. The water uptake% was plotted against the time.

3. Results and discussion

Drug recrystallization in transdermal matrix patches is detrimental for the drug release and should be prevented. Especially very lipophilic matrices, like polyisobutene (PIB), show compatibility issues with some commonly used crystallization inhibitors. Therefore, the incorporation of adsorbates onto insoluble carriers into matrix patches could be an alternative.

3.1. Solubility considerations

MM-PIB, the adhesive base of the patches, is a very lipophilic polymer as it consists only of isobutene units. It is not soluble in oxygenated solvents (e.g. low molecular weight esters, ketones and alcohols) but in paraffinic solvents like hexane [33,34] or in chloroform. Ethinyl estradiol and levonorgestrel were practically insoluble (according to USP 24 categories) in water and hexane (Table 2). While ethinyl estradiol showed good solubility in several organic solvents, levonorgestrel was only sparingly or slightly soluble in all but chloroform. Hence, chloroform was used for the preparation of both the adsorbates and the casting mixtures to prevent the recrystallization of levonorgestrel as a result of its insolubility in the process solvent.

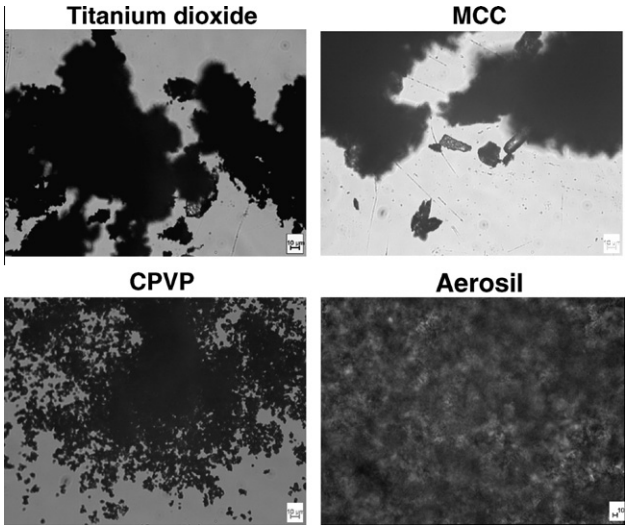

Fig. 1. Polarized light microscopic investigation of adsorbates containing 1.0% levonorgestrel and 0.2% ethinyl estradiol content onto titanium dioxide, MCC, CPVP and Aerosil.

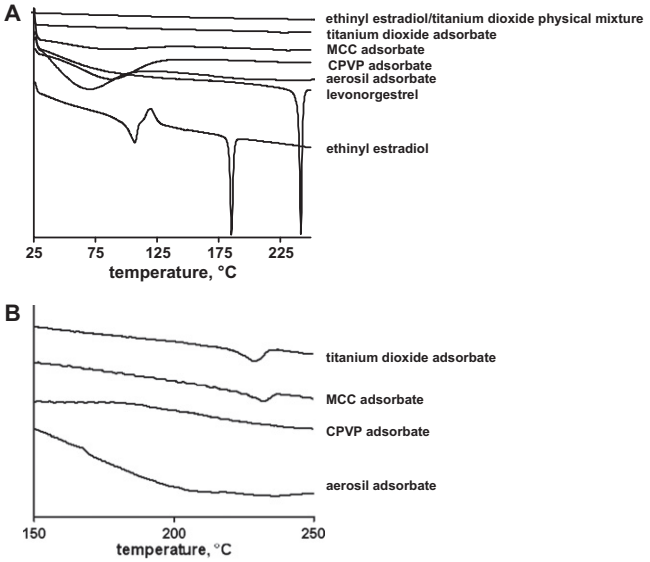

Fig. 2. DSC thermograms of ethinyl estradiol and levonorgestrel recrystallized from chloroform, adsorbates with 1.0% ethinyl estradiol and 5.0% (w/w) levonorgestrel onto Aerosil, CPVP, MCC and titanium dioxide and a physical mixture of titanium dioxide and ethinyl estradiol (1.0%) (A), magnification of the DSC thermograms of the adsorbates (B).

Table 3
DSC data of adsorbates containing 1.0% ethinyl estradiol and 5.0% levonorgestrel onto different adsorbents.

Adsorbent	Ethinyl estradiol			Levonorgestrel		
	Melting point (°C)	Enthalpy of fusion (J/g)	Crystallinity (%)	Melting point (°C)	Enthalpy of fusion (J/g)	Crystallinity (%)
Pure drug	184.9	81.1	100.0	241.2	128.6	100.0
Titanium dioxide	b.d.l.	b.d.l.	n.d.	228.2	2.9	45.9
MCC	b.d.l.	b.d.l.	n.d.	231.3	1.8	28.2
CPVP	b.d.l.	b.d.l.	n.d.	-	0	0
Aerosil	b.d.l.	b.d.l.	n.d.	-	0	0

b.d.l.: below detection limit; n.d.: not determined.

3.2. Suitability screening of insoluble carriers

3.2.1. Influence of the carrier on the drug physical state

In the first step, adsorbates of ethinyl estradiol and levonorgestrel (drug content: 1.0% and 5.0%, w/w, respectively) onto titanium dioxide, Aerosil, MCC and CPVP were prepared and the carrier's ability to inhibit drug recrystallization was investigated. Polarized light microscopy revealed the presence of drug crystals in the adsorbate onto titanium dioxide and the absence of drug crystals in the adsorbates onto CPVP and Aerosil. It was not possible to determine the presence or the absence of drug crystals in adsorbates onto MCC with this method because the carrier itself is crystalline (Fig. 1). DSC scans of pure ethinyl estradiol (recrystallized from chloroform) showed a melting transition at 108.0 °C, which was probably related to a hydrate form of the drug [35] (Fig. 2A). The hydrate form recrystallized immediately afterwards

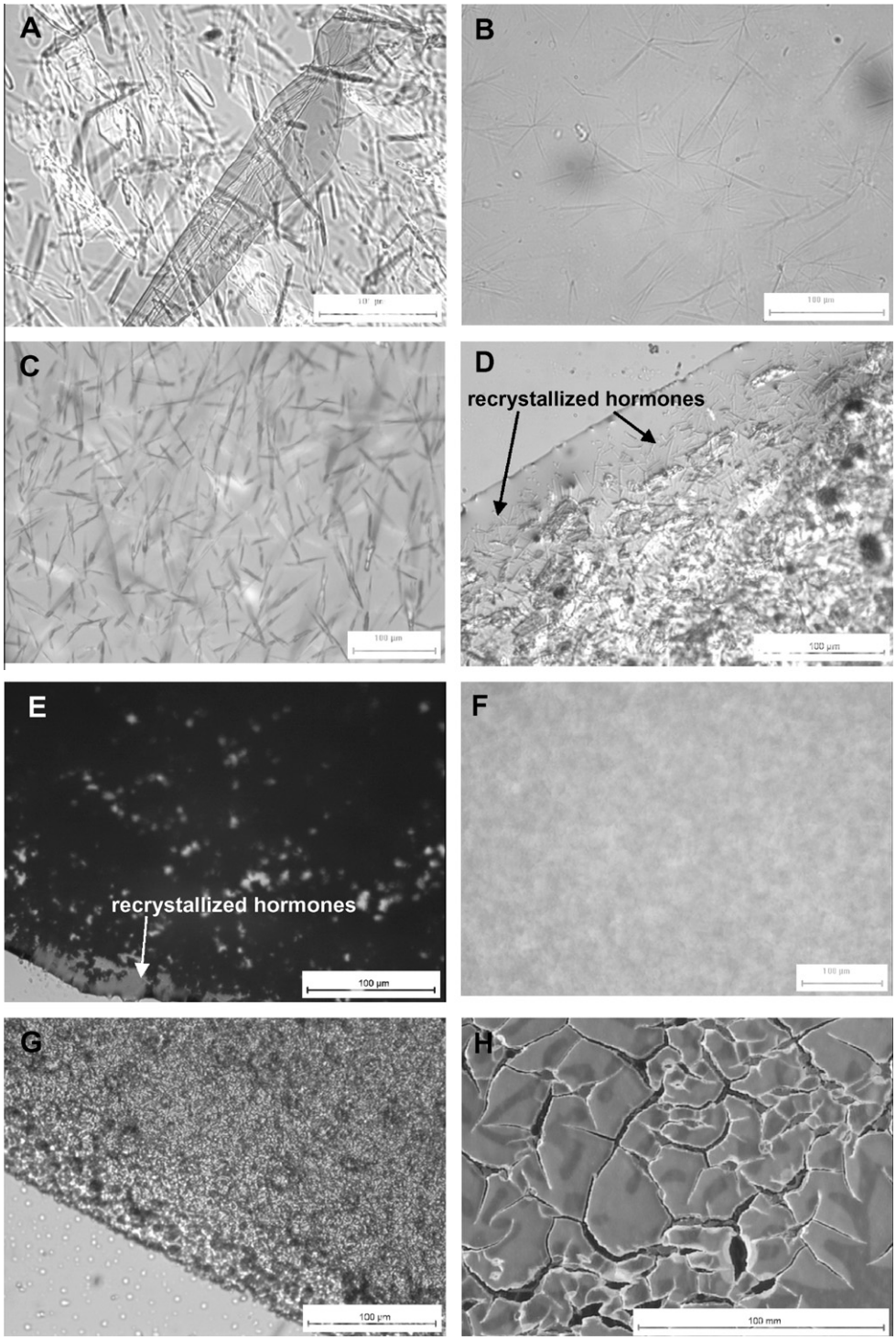

Fig. 3. Polarized light microscopic investigation of MM-PIB matrices containing 1.0% levonorgestrel (A), 0.2% ethinyl estradiol (B), 0.2% ethinyl estradiol and 1.0% levonorgestrel (C) and adsorbates with 0.2% ethinyl estradiol and 1.0% levonorgestrel onto 20% MCC (D), 20% titanium dioxide (E), 20% CPVP (F), 20% Aerosil (G) 20% Aerosil (macroscopic picture (H)).

and melted at 184.9 °C. Pure levonorgestrel (recrystallized from chloroform) showed only one melting transition at 241.2 °C.

DSC scans of a physical mixture containing ethinyl estradiol and titanium dioxide (drug content: 1.0%, w/w) were not able to detect ethinyl estradiol's melting peak. Hence, this method was not sensitive enough to draw conclusions with regard to ethinyl estradiol's physical state in the adsorbates. Drug adsorbates onto MCC and titanium dioxide showed levonorgestrel's melting transition at 231.3 and 228.2 °C, respectively (Fig. 2B. The melting peak depression in comparison with the pure levonorgestrel has been described in the literature for adsorbates. It was attributed to drug–carrier interactions and the minuscular form of the drug crystals, which facilitates their melting [21,30]. Adsorbates onto CPVP and Aerosil did not show thermal events related to the melting of levonorgestrel. By correlating the adsorbates' enthalpy of fusion to the pure drug's enthalpy of fusion, levonorgestrel's crystallinity in adsorbates with titanium dioxide and MCC was calculated to be 45.9% and 28.2%, respectively (Table 3).

Hence, the ability of the adsorbents to inhibit the recrystallization of levonorgestrel increased in the order of titanium dioxide < MCC < CPVP = Aerosil. No conclusion could be drawn for the physical state of ethinyl estradiol due to its low loading. It is likely that the formation of hydrogen bonds between the carriers and the drugs was responsible for the crystallization inhibition. Both drugs contain moieties able to act as hydrogen acceptors (carbonyl and hydroxyl groups) or hydrogen donors (hydroxyl groups). CPVP possesses a carbonyl group which can act as hydrogen acceptor [33]. MCC's 1,4 β-acetal and the hydroxyl groups enable its contribution in hydrogen bonds. Oguchi et al. [27,33] investigated the crystallinity of benzoic acid after grinding with MCC and found reduced crystallinity, which they attributed to the formation of hydrogen bonds. The ability of titanium dioxide to act as hydrogen acceptor has been described by Diebold [32]. Aerosil's silanol groups are capable of forming hydrogen bonds with drugs, which has been investigated by Monkhouse and Lach [36] and Watanabe [23]. Interactions between drug and carrier are thought to play a major role for drug recrystallization inhibition because they immobilize the drug molecules [10].

The second step was the incorporation of the adsorbates into the adhesive matrix to form transdermal patches. As a comparison, transdermal patches with similar drug loading were prepared without adsorbents. The crystal-free casting solution for these patches was prepared by adding chloroformic drug solution to the chloroformic MM-PIB solution.

It was not possible to detect drug crystals in patches by DSC or XRD because the total drug concentrations (0.2% and 1.0% for ethinyl estradiol and levonorgestrel, respectively) were below the detection limit. Hence, the patches were investigated by polarized light microscopy.

Patches without adsorbents containing 0.2% ethinyl estradiol and 1.0% levonorgestrel showed drug crystals. To identify whether these crystals were ethinyl estradiol or levonorgestrel, patches with solely 0.2% ethinyl estradiol and patches with solely 1.0% levonorgestrel were prepared. Since these patches also showed crystals (Fig. 3A–C), it was concluded that neither of the hormones was completely soluble in the adhesive matrix at the investigated concentrations. Patches containing drug adsorbates onto titanium dioxide and drug adsorbates onto MCC showed recrystallized hormones in the matrix, although to a lower extent than the patches with the pure drug (Fig. 3D and E). The drug crystals' characteristic needle-like shape upon recrystallization in the adhesive matrix enabled their distinction from MCC crystals. Latsch et al. [37] showed that the crystallization process of the norethindrone acetate in a matrix patch was considerably accelerated when a second steroid (estradiol hemihydrate) was present. Therefore, it can be speculated that both hormones recrystallized to a certain extent in the matrices containing drug-titanium dioxide and drug-MCC adsorbates. MM-PIB films prepared with adsorbates onto CPVP and Aerosil did not show drug crystals (Fig. 3F and G). It was not possible to prepare coherent patches with the Aerosil adsorbate, because its addition to the MM-PIB solution caused the formation of a thixotropic gel. This mixture had to be diluted with chloroform to become castable. This diluted solution, however, yielded an incoherent film without adhesive properties (Fig. 3H). Therefore, patches based on Aerosil adsorbates were not further investigated.

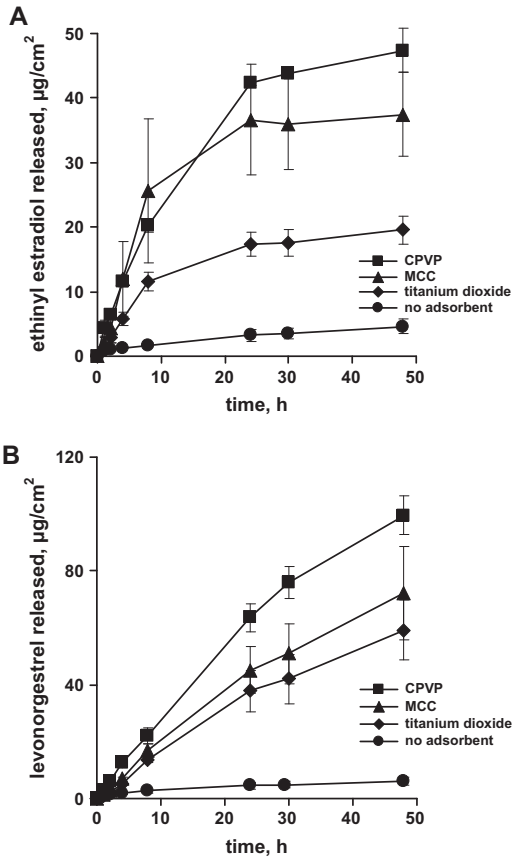

Fig. 4. Effect of adsorbent type on the ethinyl estradiol (A) and levonorgestrel (B) release from MM-PIB patches containing ethinyl estradiol (0.2%) and levonorgestrel (1.0%) or the same amount of drugs adsorbed onto CPVP, MCC or titanium dioxide (20%).

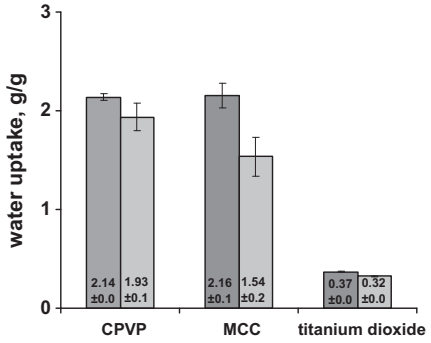

Fig. 5. Water uptake (g water/g adsorbent) of CPVP, MCC and titanium dioxide determined by centrifugation of an aqueous suspension (left column: 3 min at 5000 rpm; right column: 15 min at 13,000 rpm and incubation for 12 h before the decantation).

3.2.2. Influence of the carrier on the drug release

The release of both ethinyl estradiol and levonorgestrel from patches containing adsorbates was higher than from patches without adsorbent and increased in the order of titanium dioxide < MCC < CPVP (Fig. 4).

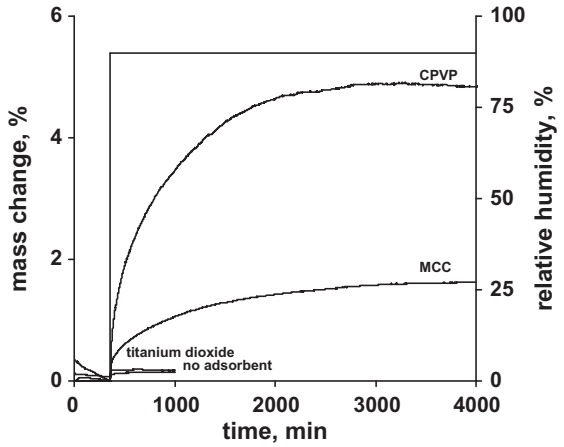

Fig. 6. Effect of adsorbent type on the water uptake at 90% RH of MM-PIB patches containing ethinyl estradiol (0.2%) and levonorgestrel (1.0%) or the same amount of drugs adsorbed onto CPVP, MCC or titanium dioxide (20%).

Since the water uptake of a matrix can influence the drug release, it was determined for the adsorbents and the manufactured patches. The adsorbent's water uptake as a bulk property was determined by centrifuging aqueous adsorbent suspensions and weighing the centrifuge residue thereafter. The use of mild centrifugation conditions (3 min, 5000 rpm) resulted in increasing water uptake in the order of titanium dioxide < MCC = CPVP (Fig. 5). Rigorous centrifugation conditions (15 min, 13,000 rpm) followed by the incubation of the centrifugation vessels for 12 h before the decantation showed a significantly higher water uptake of CPVP than of MCC. The difference was probably a result of CPVP's higher swelling pressure compared to MCC which led to a greater expansion of the particles during the incubation period. Conventional methods to determine the water uptake of dosage forms are not suited for transdermal patches due to their stickiness. Therefore, a dynamic vapor sorption (DVS) method was developed, which determined the dried patches' weight gain at 90% RH as a surrogate parameter. While patches without adsorbates and patches with adsorbates onto titanium dioxide did not show a significant water uptake, patches with adsorbates onto MCC and CPVP took up approximately 1.6% and 4.8% water, respectively (Fig. 6). Thus, the difference in water uptake between the adsorbates became more pronounced when they were restricted by the adhesive matrix, which was likely due to their different swelling pressures.

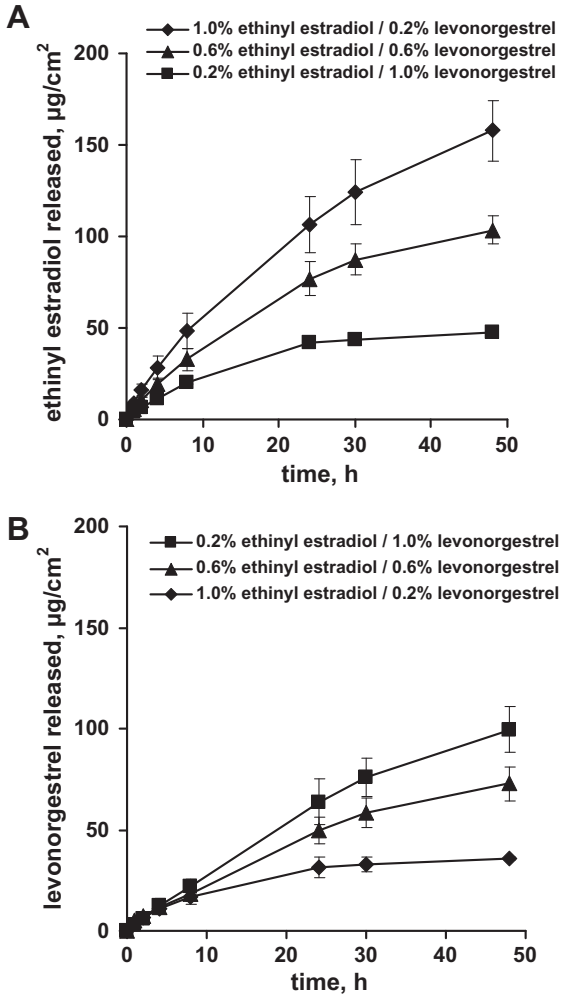

Fig. 7. Effect of ethinyl estradiol and levonorgestrel content on the ethinyl estradiol (A) and levonorgestrel (B) release from MM-PIB patches containing adsorbates of the drugs onto CPVP (20.0%).

3.3. Patches containing adsorbates onto crospovidone

Patches containing adsorbates onto CPVP showed the most pronounced increase in drug release and were crystal free. Therefore, they were investigated in more detail.

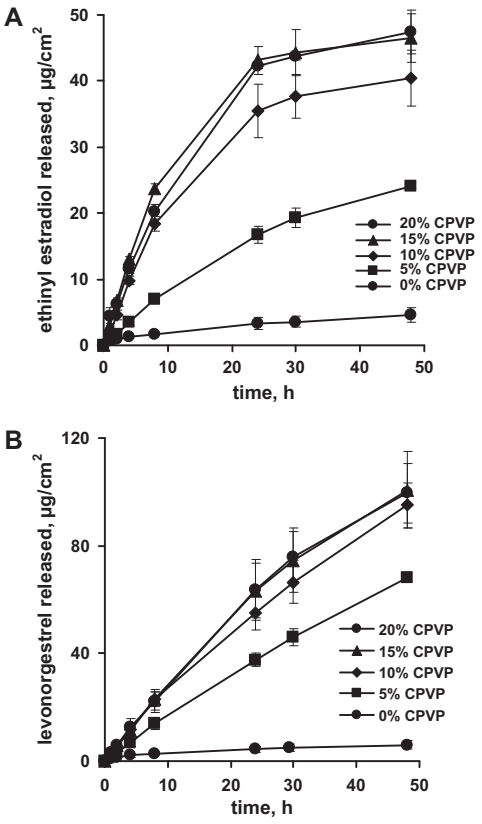

Fig. 8. Effect of CPVP content on the ethinyl estradiol (A) and levonorgestrel (B) release from MM-PIB patches containing ethinyl estradiol (0.2%) and levonorgestrel (1.0%).

3.3.1. Effect of drug and drug loading

Patches with CPVP adsorbates containing different drug loadings of ethinyl estradiol and levonorgestrel at a constant CPVP content were investigated. No crystals could be detected in the patches by polarized light microscopy. The drug release increased with drug loading (Fig. 7) for both drugs. Levonorgestrel was released slower than ethinyl estradiol, probably as a result of levonorgestrel's lower solubility in the release medium (Table 2). In other words, the release medium that penetrated into the patch was closer to the saturation concentration of levonorgestrel than of ethinyl estradiol, which could have slowed down the dissolution of levonorgestrel.

3.3.2. Effect of the crospovidone content

Patches with 1.0% levonorgestrel and 0.2% ethinyl estradiol content were crystal free at a CPVP content of 10% or higher (which corresponded to a drug loading of 12% onto CPVP). Drug crystals could be detected by polarized light microscopy in matrices with 5% CPVP content. This result was in agreement with findings obtained from carbamazepine-CPVP systems in which a carbamazepine loading of 9.1% yielded crystal-free formulations (these results will be published elsewhere).

The drug release increased with increasing CPVP content (Fig. 8). This was probably due to two reasons: Firstly, the drugs were (partly) crystalline in formulations without CPVP or with 5% CPVP which slowed down their dissolution. Secondly, the incorporation of CPVP into the MM-PIB matrix is likely to increase the diffusion coefficient of the drugs by forming fluid-filled channels between the CPVP particles upon water uptake. According to the Stokes–Einstein equation, the diffusion coefficient is inversely proportional to the viscosity and hence higher in the release medium than in the adhesive matrix. While in formulations without CPVP, drug molecules had to travel through the viscous polymer matrix and they could travel through areas of release medium that surrounded the CPVP particles in patches containing adsorbates onto CPVP. Higher CPVP contents (up to 15% CPVP) resulted in a more connected CPVP network which increased the release. Formulations with 15% and 20% CPVP adsorbate released the drugs almost identically. The reason for the slower ethinyl estradiol release of patches containing 15% and 20% CPVP was the depletion of the drug (at 48 h these patches had released approximately 81% of the drug).

3.3.3. Effect of crospovidone particle size

Smaller CPVP particles led to faster drug release in the beginning (0–24 h, Fig. 9), while the drug release from patches with bigger CPVP particles was slower in the beginning but did not level off later (24–48 h). This result was probably due to the particle distribution in the patch. Microscopic pictures of the patch cross-sections showed that smaller CPVP particles were distributed evenly throughout the patch. In contrast, larger CPVP particles

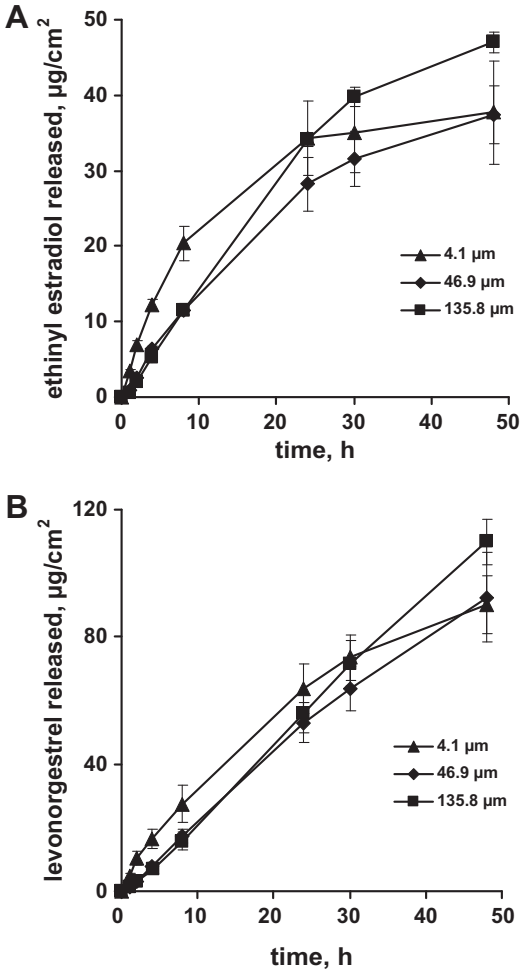

Fig. 9. Effect of CPVP particle size on the ethinyl estradiol (A) and levonorgestrel (B) release from MM-PIB patches containing ethinyl estradiol (0.2%) and levonorgestrel (1.0%) adsorbed onto CPVP (20%).

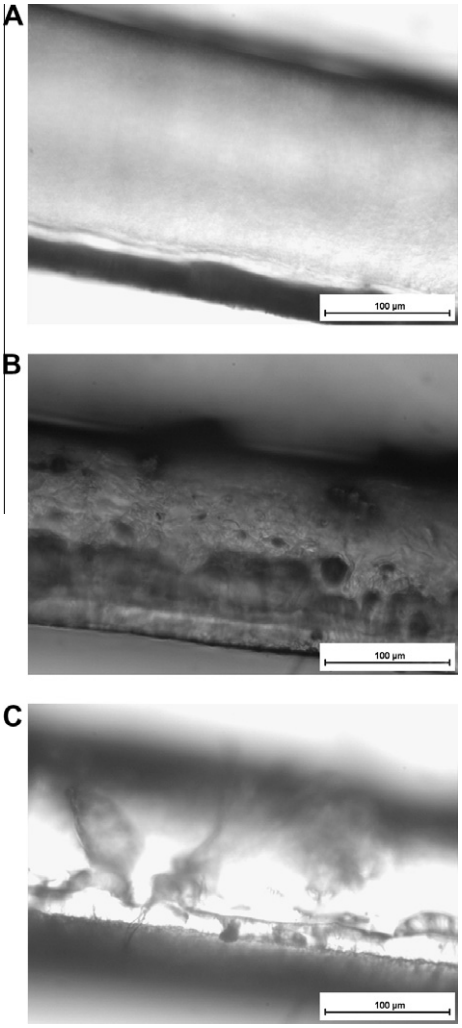

Fig. 10. Cross-sections of patches containing ethinyl estradiol (0.2%) and levonorgestrel (1.0%) adsorbed onto CPVP (20%) with d_{50} = 4.1 µm (A), 46.9 µm (B) and 135.8 µm (C).

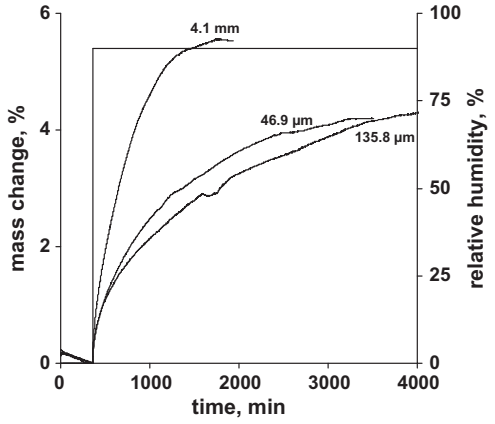

Fig. 11. Effect of the CPVP particle size on the water uptake at 90% RH of MM-PIB patches containing ethinyl estradiol (0.2%) and levonorgestrel (1.0%) adsorbed onto CPVP (20%).

occupied the area close to the release side of the patch to a lesser degree (Fig. 10). In the initial drug release, phase patches containing smaller CPVP particles probably released rapidly because the adsorbates were present at the release surface. In contrast, the release medium needed more time to reach the adsorbate in patches containing larger CPVP particles, which was reflected by their slower water uptake determined by DVS (Fig. 11). This slowed down the initial release from patches containing adsorbates onto larger CPVP particles. However, once the release medium reached the CPVP particles, they could release the drugs relatively fast because drug diffusion could occur through large areas of swollen CPVP in the patch without intermittent MM-PIB matrix.

4. Conclusion

The incorporation of adsorbates onto crospovidone into medium molecular weight polyisobutene matrices yielded crystal-free patches with significantly increased drug release. Besides the molecularly dispersed state of the drugs, this was probably a result of the increased water uptake of the matrices governed by CPVP.

In most cases, the stratum corneum is the rate determining barrier for transdermal drug delivery. The skin permeation of drugs from the formulations has yet to be investigated.

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