Development of a predictive model for the stabilizer concentration estimation in microreservoir transdermal drug delivery systems (MTDDS) using lipophilic pressure sensitive adhesives as matrix/carrier

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ABSTRACT

Microreservoir-type transdermal drug delivery systems (MTDDS) can prevent drug crystallization; however no current predictive model considers the impact of drug load and hydration on their physical stability. We investigated MTDDS films containing polyvinylpyrrolidone (PVP) as polymeric drug stabilizer in lipophilic pressure sensitive adhesive (silicone). Medicated and unmedicated silicone films with different molar N-vinylpyrrolidone (VP):drug ratios were prepared and characterized by FTIR, differential scanning calorimetry (DSC), scanning electron microscopy (SEM), microscopy, Dynamic Vapour Sorption (DVS) and stability testing for four months at different storage conditions. Homogeneously distributed drug-PVP associates were observed when non-aqueous emulsions, containing drug-PVP (inner phase) and silicone adhesive (outer phase) were dried to films. DVS data was essential to predict physical stability at different humidities. A predictive thermodynamic model was developed based on drug-polymer hydrogen-bonding interactions, using the Hoffman equation, to estimate the drug-PVP ratio needed to obtain stable MTDDS and to evaluate the impact of humidity on their physical stability. This new approach considers the impact of polymorphism on drug solubility by using easily accessible experimental data ($T_m$ and DVS) and avoids uncertainties associated with the solubility parameter approach. In conclusion, a good fit of predicted and experimental data was observed.

KEY WORDS

Polymeric drug delivery system, transdermal, solid dispersion, amorphous, physical stability, thermal analysis, hydration, water sorption, thermodynamics, mathematical model
ABBREVIATIONS AND SYMBOLS

\( a \) activity
API active pharmaceutical ingredient
ASA acetylsalicylic acid
DIA drug-in-adhesive
DSC differential scanning calorimetry
DVS dynamic vapor sorption
FTIR Fourier transform infrared spectroscopy
GC gas chromatography
HPLC high performance liquid chromatography
IBU ibuprofen
\( K \) equilibrium constant
LM light microscopy
MTDDS Microreservoir-type Transdermal Drug delivery System
m mass
M molecular weight
n molar quantity
PDMS polydimethylsiloxane
PSA pressure sensitive adhesive
PVP polyvinylpyrrolidone
RH Relative humidity
SAA salicylic acid
\( T \) Temperature
\( T_g \) glass transition temperature
\( T_m \) melting temperature
TDDS transdermal drug delivery systems
VP vinlypyrrolidone (monomer unit of PVP)
\( x \) (or \( X \)) molar fraction
\( \alpha \) mass fraction of inner phase
\( \alpha \) interaction coefficient
\( \delta \) solubility parameter
\( \Delta G_H \) Gibbs free energy of hydrogen bonding
\( \Delta G_m \) Gibbs free energy of mixing
\( \Delta G_v \) Change of Gibbs free energy upon crystallization
\( \Delta H_f \) (or \( \Delta H_{fus} \)) Enthalpy of fusion
\( \phi \) volume fraction
\( \chi \) Flory-Huggins interaction parameter
INTRODUCTION

Transdermal Drug Delivery Systems (TDDS) for passive drug delivery can be formulated using either lipophilic (e.g. silicone and polyisobutylene) or polar (e.g. acrylic) pressure sensitive adhesives (PSAs). In the case of acrylic drug-in-adhesive (DIA) patches, H-bonding interaction between the drug molecules and the polar groups of the adhesive polymer chain can have a stabilizing effect by preventing drug crystallization\(^1\). Such a stabilizing effect is not possible when lipophilic PSAs are used for the formulation of DIA films, therefore the incorporation of a stabilizing excipient in the PSA is necessary. Hydrophilic polymeric drug carriers, such as PVP\(^2,3\), polyethylene glycol\(^4\) or poloxamer\(^5\), have been used in lipophilic and polar adhesives both to increase the drug loading capacity, thus drug activity during patch application, and to prevent drug crystallization during storage. For example, PVP was found to be effective with captopril and levonorgestrel in acrylate and silicone adhesives\(^6\).

It has been shown for polar (acrylic) PSA that the method of incorporation of the stabilizer in the DIA film has an effect on the stability of the formulation\(^5\). In the case of lipophilic PSAs, incorporation of the hydrophilic drug/polymer binary mixture within the PSA, results in the formation of a microreservoir system. Microreservoir-type transdermal drug delivery systems (MTDDS) are dispersions of microscopic drug reservoirs (spheres)\(^7,8\) within the polymer matrix\(^9\).

In the manufacturing process of MTDDS the drug is at first dissolved in a solution of the water-soluble polymer. This solution is then homogeneously dispersed in a lipophilic polymer\(^10\). The term “Microreservoir System” has been used for different marketed TDDS like Nitrodisc®, containing nitroglycerin dissolved in a liquid inner phase of a non-adhesive silicone matrix, and Neupro® containing a non-crystalline rotigotine/PVP dispersion in a silicone adhesive film\(^9\). Studies of the interactions between PVP and drugs have been published for diverse other formulations\(^11–13\). These studies were more focused on evaluation of the drug release properties from the microreservoirs rather than on thermodynamics and physico-chemical properties of such type of TDDS\(^9,14–16\).

In this paper, the term “microreservoir” describes an amorphous polymeric drug carrier dispersion in a silicone matrix. Three aromatic carboxylic acids, ibuprofen (IBU), salicylic acid (SAA) and aspirin (acetylsalicylic acid; ASA) were selected to investigate the suitability of different grades of PVP to serve as a polymeric drug carrier for these acids in a silicone pressure sensitive adhesive (PSA) suitable for use in MTDDS (Figure 1). The MTDDS design has already been successful in sustaining the stability of rotigotine (Neupro®)\(^17\) which is a weak base.
The aim of this work was to develop and evaluate a predictive model for the estimation of PVP concentration in MTDDS which can be used to define boundary conditions for the inhibition of drug crystallization at pre-formulation stage. The novelty of our proposed approach is that it considers not only the effect of drug/polymer H-bonding interaction but also the effect of hydration on the physical stability of the MTDDS. Similar to our previous paper our thermodynamic approach provides a combination of theoretical estimations with experimentally measured thermal and moisture uptake properties, leading to a novel predictive equation.

MATERIALS AND METHODS

Materials

**Amine compatible silicone adhesives** in ethyl acetate (BIO-PSA 7-4302 and BIO-PSA 7-4202) were obtained from Dow Corning (Midland, Michigan, USA). Low- and high-molecular-weight polyvinylpyrrolidones (Kollidon 12PF and Kollidon 90F) were purchased from BASF (Ludwigshafen, Germany). SAA, ASA and sodium metabisulfite were acquired from Sigma-Aldrich (St Louis, MI, USA) and IBU from Knoll Pharmaceuticals (Nottingham, UK). Ethyl acetate, acetonitrile, methanol and ethanol were all HPLC grade and purchased from Fisher Scientific (Fair Lawn, New Jersey, USA), along with acetic acid and phosphoric acid. Release liner Scotchpak 9755 and backing liner Scotchpak 9735 were supplied by 3M (St Paul, USA).

Methods

**Estimation of solubility parameters, drug solubility in silicone adhesive and driving force for drug crystallization**

Solubility parameters $\delta$ of drugs and polymers were determined using Synthia software (Material Studio, Accelry’s) The Synthia software can provide solubility parameter values based on the van Krevelen and Fedors group contribution methods. In our study we used the Fedors values because of the unpolar character of the matrix adhesive.

This software allows the calculation of $\delta$ after input of the repeat units of a polymer, thus, drug structures were each entered as monomer units considering that the resulting solubility parameter does not depend on the input molecular weight. For example in the case of ibuprofen, hydrogen atoms bonded to carbon atoms were chosen as head and tail atoms. Regarding end-capped silicone
polymers, calculations were performed for a composition of 57.5% (w/w) of resin and 42.5% (w/w) of polydimethylsiloxane (PDMS).

The drug mass fraction solubility in PSA was estimated using the regular solution theory equation, Equation (1), by assuming that the drug mass fraction solubility can be approximated by $x_2$ and that the polymer volume fraction $\phi_1 \approx 1$. The derivation of this equation is explained in our previous paper$^1$.

$$\ln(x_2) = -\frac{\Delta H_{fus} (T_m - T)}{RT_{m}} - \frac{v_2 \phi_1^2}{RT} \times (\delta_1 - \delta_2)^2$$

The driving force for drug recrystallization, i.e. the chemical energy gained by the phase transition from the amorphous to the crystalline state, was calculated using the Hoffman equation as explained in our previous paper$^1$.

**Determination of solid content of liquid adhesives**

The solid content of liquid adhesive was measured gravimetrically as per Wolff et al.$^{19}$ Results were verified by examination of residual solvent using Headspace Gas Chromatography as described in the following section. The mean value of solid content (% w/w) was used for the calculation of the required amount of liquid adhesive for each target drug and/or PVP loads in the films.

After measuring the solids content of silicone 7-4302 and 7-4202, a mixture containing 50%(w/w) solids of each PSA was prepared. Accurate masses of BIO PSA 7-4302 and BIO PSA 7-4202 were stirred together overnight, using mechanical stirring (IKA, Staufen, Germany) at 150 rpm. Solids content of that solution was then measured.

**Residual solvent analysis**

Residual solvent in dry adhesive, binary mixtures, drug-in-adhesive (DIA) and microreservoir films was determined by Headspace Gas Chromatography (GC) (Agilent Technologies 7890A, Santa Clara, CA, USA) using the method described in our previous paper$^1$. Ethanol and ethyl acetate are class 3 solvents and their overall concentration in pharmaceutical products should be less than 5000ppm (or 0.5% (w/w))$^{20}$. As MTTDS could contain two residual solvents and to
make sure that overall residues were below the limit of 0.5%, the target upper limit of solvent residues (for each solvent) was set at 0.2%(w/w).

Calibration curves were prepared using five solutions of ethanol and ethyl acetate in internal standard (toluene) for the quantification of solvent residues in dry adhesive, DIA and microreservoir films and for the quantification of ethanol in dried binary mixture samples.

Total solvent residues were less than 0.2%(w/w) in every sample (binary mixtures, and MTDDS).

**Determination of drug concentration using HPLC**

*Measurement of ibuprofen content*

Ibuprofen content was measured using a Phenomenex Luna C8 column (4.6 x 150 mm; 5 μm particle size, Phenomenex, Torrance CA). The mobile phase was a mixture 45:55 acetonitrile: 0.01M phosphoric acid, at a flow rate of 2 ml.min⁻¹. Detection was performed using a diode array detector at a wavelength of 220nm. The injection volume was 5μl. A calibration curve was prepared for the quantification of IBU using a stock solution of 42.6mg pure IBU in 25ml of a 50:50 ethyl acetate:acetonitrile solution. Samples were prepared by dissolving 5cm² of dry film in 2ml of a 50:50 ethyl acetate:acetonitrile followed by sonication. The solution was then introduced in filter vials (Thomson 355-38-100 Filter vial 0.2µm, nylon, Thomson Instrument Company, Cleveland, USA). All samples were examined in triplicate (n = 3). Retention time was 7.0 min for IBU.

*Measurement of salicylic acid and acetylsalicylic acid contents*

Salicylic acid and acetylsalicylic acid contents were measured using high performance liquid chromatography (HPLC, 1290 Infinity, Agilent Technologies, Santa Clara, CA, USA) and a Phenomenex Luna C18 column (4.6 x 150 mm; 5 μm particle size, Phenomenex, Torrance CA). The mobile phase was a mixture 70:30 of a 3% (v/v) solution of acetic acid in water and 3% (v/v) solution of acetic acid in methanol, at a flow rate of 1.5 ml.min⁻¹. Detection was performed using a diode array detector at a wavelength of 275 nm. The injection volume was 5 μl. A calibration line was prepared for the quantification of salicylic acid using a stock solution of 49.8 mg of pure SAA in 25ml of 50:50 ethyl acetate:formic acid in methanol (5:95). Similar calibration curve was prepared for the quantification of ASA. Samples were prepared by dissolving an accurately weighed 5 cm² of dry film in 2 ml of a 50:50 mixture of ethyl acetate: formic acid (5% (v/v)) in
methanol. All samples were examined in triplicate \((n = 3)\). Retention time was 10.0 min for SAA and 5.6 min for ASA.

**Preparation of drug-PVP binary mixtures**

To examine the stability of drug and PVP binary mixtures, drug and PVP were dissolved at different ratios (VP:drug molar ratio 1:1, 2:1, 3:1, 4:1, and also 1:2 in the case of ibuprofen) in ethanol. The ethanol content was fixed at 80% (w/w) for Kollidon 90F and 50%(w/w) for Kollidon 12PF (65%(w/w) for mixtures of K12 and ASA). The solutions were coated on a 3M Scotchpack 9755 release liner, on the side not coated with a fluoropolymer, on an Erichsen Model 509/1 film coater (Hemer-Sundwig, Germany) as explained in our previous paper.\(^1\) The knife blade was set to the height of 510 µm.

The casted films were then dried using a universal oven (Memmert Model UNE 400, Schwachbach, Germany) at controlled temperature and samples \((n=3)\) were punched from each dried film and analyzed using headspace gas chromatography to determine solvent residues. Drying conditions were adjusted so that residual solvents did not exceed 0.2%(w/w). Optimized drying conditions were found to be 15 min at 50°C.

**Drug solubility in the adhesive**

In order to get an estimate of the drug saturation solubility in the dry silicone adhesive, medicated adhesive films were prepared with three different target drug concentrations ranging from 0.1% to 5% (w/w). Drug and liquid adhesive were accurately weighed (Mettler PJ400, Mettler, Greifensee, Switzerland) in a tared container and mixed at about 150 rpm overnight, using an overhead stirrer (IKA, Staufen, Germany). The solution was then coated and dried as described previously and three films were prepared per solution. Mean film thicknesses ranged from 66 to 78µm (film coating weights from 5.6 to 7.2 mg.cm\(^{-2}\)). 20cm\(^2\) samples \((n=3)\) were then punched from each film and analyzed using headspace gas chromatography to verify that solvent residues did not exceed 0.2%(w/w).
Preparation of microreservoir films

Unmedicated and medicated microreservoir films (15cm in width and about 30 cm in length) were prepared using an adhesive solution 50/50 mixture of BIO-PSA 7-4302 and 7-4202, as explained below:

**Unmedicated.** Two solutions of PVP in ethanol were prepared with solids content adjusted according to PVP viscosity; 20% (w/w) for K90 and 50% (w/w) K12.

They were mechanically stirred overnight at 200 rpm using an over-head stirrer (IKA, Staufen, Germany).

For each PVP grade, three non-aqueous emulsions were prepared at 4.9, 5.3 and 6.4%(w/w) of PVP (dry mass). An accurately weighed mass of solution was introduced into a beaker, to which an accurate mass of silicone adhesive solution was added leading to emulsification. The emulsion was homogenized (Silverson Machine Ltd., Waterside, Bucks, UK) for one minute and then coated and dried as detailed previously.

**Medicated.** Five non-aqueous emulsions were prepared for each drug, their target compositions are detailed in Table 1. Solutions of drug and PVP in ethanol were prepared with solids content of 20%(w/w) or 50%(w/w), for preparations containing K90 or K12, respectively, as explained above. The solutions were stirred overnight at 200 rpm. A non-aqueous emulsion was then prepared for each solution by mixing an accurately weighed mass of solution with an accurate mass of silicone adhesive solution. The emulsion was homogenized (Silverson Machine Ltd., Waterside, Bucks, UK) for one minute and then coated and dried as detailed previously.

The mean coating weight \(n = 3\) or 4) and film thickness \(n = 5\) were measured per film (intra-film mean) and then averaged (inter-film mean, \(n = 3\)).

**Table 1.** Composition of manufactured MTDDS (average film thicknesses ranging from 57 to 78\(\mu\)m for films containing K90 and from 62 to 69\(\mu\)m for films containing K12, with film coating weights ranging from 4.1 to 5.8mg.cm\(^{-2}\) and from 5.0 to 6.7mg.cm\(^{-2}\) respectively). Drug load was confirmed via HPLC.
**Fourier Transform Infrared Spectroscopy (FTIR)**

FTIR spectra of pure products, dried binary mixtures and dry films were obtained using a Spectrum BX FTIR Spectrometer (Perkin Elmer, Massachusetts, USA) with a Horizontal Attenuated Total Reflectance (HATR) sampling accessory. The resolution was set to 4 cm$^{-1}$. A background scan was initially run and the samples were then scanned 8 times from 550 to 4000 cm$^{-1}$ and analyzed using Spectrum v5.3.1.

**Differential Scanning Calorimetry (DSC)**

Examination of the thermal behavior of pure compounds, binary mixtures and adhesive films was carried out with a DSC Q1000 (TA Instrument, USA) purged with dry nitrogen (50 ml/min). Calibration of the instrument was established using indium standard.

Samples were accurately weighed using a microbalance (Mettler MT5, Mettler-Toledo, Greifensee, Switzerland) and introduced into aluminium hermetic pans and lids. Standard heat/cool/heat cycles (heating rate of 5°C/min or 10°C/min and cooling rate of 5°C/min) were performed in triplicate at -70 °C → 200 °C → -70°C or at 20 °C → 180 °C → 20°C for silicone films containing SAA. Melting points and enthalpies of fusion were recorded from the melting endotherms of the first heat, whereas glass transition temperatures ($T_g$) were recorded from the second heat.

**Microscopy**

*Polarized microscopy*: Dried binary mixtures and medicated films were observed under a microscope (Olympus BH-2, Olympus Corporation, Tokyo, Japan) fitted with a 10x magnification lens, a camera (AxioCam, MRc, Carl Zeiss, UK) and AxioVision vs4.4 software. Polarized light was used in order to determine whether the particles observed were crystalline. The scale of the microscope was calibrated for each magnification using graticules of 1mm.

*Optical microscopy*: Fresh non aqueous emulsions and microreservoir films were observed using optical microscopy (Olympus BH-2, Olympus Corporation, Tokyo, Japan) fitted with a 40x and a 100x magnification lenses, a camera and ScopeImage 9.0(×5) software. The scale of the microscope was calibrated for each magnification using graticules of 1mm. The diameters of at least 300 droplets were measured with ScopeImage 9.0. Diameters were analyzed statistically and
their average, median, standard deviation, frequency, %cumulative oversize and undersize distributions were determined using Excel.

**Scanning Electron Microscopy (SEM):** SEM imaging was carried out for IBU loaded silicone films, IBU loaded microreservoir silicone films and unmedicated microreservoir silicone films at a concentration of PVP corresponding to the PVP concentration of IBU loaded silicone microreservoir films (5.3%(w/w)). Images were obtained on a S3000-N scanning electron microscope (Hitachi, Rigaku, Japan) with an accelerating voltage of 30 kV. An elemental analysis was also carried with an X-Ray Link ISIS microanalysis system 7021 (Oxford Instruments, Oxford, UK).

**Dynamic Vapor Sorption (DVS)**
Dynamic vapor sorption experiments were performed on pure compounds, on medicated (VP:drug ratio 2:1) and unmedicated MTTDS using a DVS Advantage 1 instrument (Surface Measurement Systems UK Ltd., London, UK) equipped with a recording ultra-microbalance exhibiting a mass resolution of 0.1µg. A quantity of sample of typically 8 to 12mg (2 to 5mg for pure PVP) was placed into a tared aluminium pan, which was placed on the DVS pan. The temperature was maintained constant at 25 ± 0.1°C and the sample was exposed to 0.00 partial pressure (in order to record its dry mass) and then to the following water vapor partial pressure profile: 0.20, 0.40, 0.60, 0.80 and 0.90 p/p0. The partial pressure was then decreased in an identical manner to 0.00 p/p0. Each step lasted until the mass variation over time of the sample was lower than 0.002%.min⁻¹, so that the sample mass reached equilibrium. The sorption isotherms were calculated from the equilibrium mass values at each partial pressure, using the change in mass with respect to the dry mass.

The inhibition factor for hydration (in %) can be obtained by the quotient:

\[
F_{inh} = \frac{C_{water \ (unmedicated)} - C_{water \ (medicated)}}{C_{water \ (unmedicated)}} \times 100
\]

Where \( C_{water} \) represents the water content of the MTTDS (in mole %), at a given relative humidity.

For a given medicated MTTDS (e.g. VP:drug ratio of 2:1), Finh was calculated using the corresponding unmedicated MTTDS data. If it is calculated in relation to pure PVP, the PVP load should still be considered as a way to normalize the water uptake, which thus gives the same result as using the unmedicated data.
Exploratory stability studies
Samples of 20cm$^2$ each ($n = 3$) were punched from fresh binary mixture layers, DIA films and MTDDS films. Each one was stored at a different set of conditions:
- at 25.0 ± 0.6°C and at 70 ± 1% of relative humidity (RH) into a monitored oven ($c_1$),
- at ambient temperature (21 ± 2°C) and at low RH (0.9 ± 0.7%) into a cabinet (in the presence of phosphorous pentoxide) ($c_2$),
- at ambient (21 ± 2°C) temperature and ambient RH (37 ± 7%) ($c_3$).
Samples were observed at regular intervals using polarized microscopy to detect any crystallization. DSC analysis was also performed to confirm the microscopy results.

Statistical analysis
T-tests and one way analysis of variance (ANOVA) were used to analyze microscopy and DVS data using SPSS version 18 (SPSS UK Ltd, IBM, Woking, UK). Post hoc analysis was carried out with the Scheffe method and a level of significance of 95% ($p = 0.05$). When criteria of normality and homogeneity were not met, non-parametric tests were performed (Mann-Whitney).
RESULTS AND DISCUSSION

API - PVP binary mixtures

PVP was shown to be amorphous with a glass transition temperature ($T_g$) at 179.0 ± 0.3°C and 111.3 ± 3.6°C for Kollidon 90F and 12PF, respectively. The thermal properties of the three model drugs were in agreement with literature values; IBU was crystalline with a melting point at 75.9 ± 0.9°C and it converted to its amorphous form ($T_g = -43.4 ± 0.2°C$) after the first heat cycle\textsuperscript{21}. SAA showed a melting endotherm at 159.8 ± 1.1°C and a constant enthalpy of fusion even upon multiple cycles, indicative of the stability of the crystalline form\textsuperscript{21}. ASA exhibited a melting point at 143.6 ± 0.4°C and a $T_g$ at -36.9 ± 2.3°C\textsuperscript{23-26}.

Binary mixtures containing excess drug with K90 or K12 exhibited a sharp melting endotherm corresponding to drug melting point. For mixtures containing equal or greater molar amount of PVP (VP:drug = 1:1, 2:1, 3:1 and 4:1) no melting endotherm was detected. A broad glass transition temperature was observed in between the glass transition temperatures of drug and PVP for all binary mixtures, demonstrating miscibility and formation of solid solutions of drug and PVP\textsuperscript{27}, also indicative that strength of drug-drug, polymer-polymer interaction equals drug-polymer interaction. The $T_g$ value of all mixtures was in agreement with the Fox equation\textsuperscript{28}.

FTIR analysis was performed on pure compounds and binary mixtures (as shown in the case of IBU in Figure 2a). A strong band was detected on the spectra of the K90 at 1648 cm\textsuperscript{-1} (1656 cm\textsuperscript{-1} for K12) corresponding to the stretching band of the free C=O group. Pure SAA exhibited a band at 1654 cm\textsuperscript{-1} and pure IBU at 1711 cm\textsuperscript{-1}, both due to the stretching vibration of the carbonyl group\textsuperscript{29}. Pure ASA exhibited two bands at 1750 and 1681 cm\textsuperscript{-1} due to the stretching vibration of the C=O of the ester group and the carboxylic acid group, respectively\textsuperscript{30}. Those bands are sensitive to the hydrogen bonding state of the COOH functional group. Hydrogen bonding between the drug and PVP was evidenced by FTIR\textsuperscript{31} where bands corresponding to the drug carbonyl groups shifted to higher wavenumbers indicating that intermolecular drug-drug H-bonding was broken. The band corresponding to the free C=O group of the PVP (1648 cm\textsuperscript{-1} for K90) appeared on the spectra of binary mixtures containing an excess of PVP and was stronger as the VP:drug ratio increased, whereas the band at 1636 cm\textsuperscript{-1} (1630 cm\textsuperscript{-1} in the case of K12) corresponding to H-bonded C=O was weaker due to decreasing H-bonding interaction as the amount of drug in the mixture decreased.

After storage, binary films containing IBU at a VP:drug molar ratio equal or higher than 1:1 remained crystal-free, for each storage condition. In the case of SAA and ASA, crystallization was
observed on films at a VP:drug ratio of 1:1, at all storage conditions and more pronounced if RH increased.

**API – silicone PSA binary systems**

FTIR analysis on drug-in-silicone samples (Figure 2b) showed band shifts due to interaction between IBU and silicone adhesive; on the spectrum of IBU in silicone, the band corresponding to the carbonyl group of IBU at 1711 cm\(^{-1}\) shifted to higher wavenumbers, typical of H-bonded C=O. The band at 1056 cm\(^{-1}\) corresponding to the Si-O groups of silicone adhesive shifted to higher wavenumbers for IBU loaded silicone films, indicating hydrogen bonding between silicone and IBU. It was also an indication of hydrogen bonding between siloxane and residual silanol groups; otherwise this characteristic peak would have shifted to lower wavenumbers. Such effect was not observed for SAA and ASA loaded films.

Microscopy and DSC results carried on drug-in-silicone adhesive films allowed approximation of the solubility in dry silicone (Table 4). Edge effect, *i.e.* the appearance of drug crystals in the perimeter of the film, was noticed in 5% (w/w) ibuprofen-in-silicone films and was confirmed by the presence of a melting endotherm for IBU on the DSC thermogram, whereas the 1% (w/w) ibuprofen-in-silicone film remained clear and stable. Thus, saturation solubility of IBU in silicone adhesive was between 1% and 5%(w/w). 1%(w/w) SAA and ASA loaded films showed crystallization, whereas 0.1%(w/w) films remained stable. Both drugs exhibited saturation solubility between 0.1 and 1%(w/w), consequently.

**Table 2.** Physical stability of drug-in-silicone films at different storage conditions.

Prediction of drug solubility in silicone PSA was done using the limiting form of Flory-Huggins equation and the regular solution equation, as explained in our previous papers\(^{1,19}\), assuming that drug-PSA did not interact specifically, *e.g.* via acid-base reaction or defined complex formation,\(^{32}\) and also acknowledging that the Flory-Huggins equation does not take into account H-bonding interaction for solubility determination. The solubility parameter of PDMS was determined using Materials Studio to be 15 MPa\(^{1/2}\). Experimental observations of IBU and ASA solubilities in the silicone adhesive were in good agreement with the predicted solubility values calculated at 25°C using the limiting form of the Flory equation, as shown in Table 3. The relatively poor agreement between experimental solubilities and those calculated using the regular solution theory (Equation 1) was due to the facts that drug-polymer interaction unit is difficult to define and more
importantly this equation is valid for non-polar compounds and only considers endothermic mixing.

The observed deviations in the case of SAA may be explained by the fact that SAA formed strong dimer, which impacted its solubility parameter\textsuperscript{33}. The solubility parameter of SAA dimer was actually lower (22.1 MPa\textsuperscript{1/2} \textsuperscript{34,35}), as it was less available for hydrogen bonding, leading to a smaller difference in solubility parameters between drug and PSA and thus higher predicted saturation solubility. As neither of the calculated solubilities of monomeric and dimeric SAA using the Flory-Huggins equation were in agreement with the experimental results, it could be postulated that there was a mixture of monomer and dimer SAA in the DIA systems.
Table 3. Drug solubility in silicone PSA (theoretical and experimental).
MTTDS films

Unmedicated and medicated MTDDS were analyzed using FTIR. Due to low concentrations of drug and PVP in the samples, peaks were not detected.

As shown in Table 4, MTDDS films at all VP:drug molar ratios were stable. The melting endotherms exhibited in some of the films were at a suppressed melting point compared to the pure drug, indicating the decrease in the chemical potential of crystalline drug due to interaction with the polymer. The films showing a small enthalpy of fusion using DSC, showed no detectable crystals under light and polarised microscopy (× 100 magnification). So, even if these films would be described as stable based on microscopy data, they were metastable when DSC data was considered. No glass transition was detected on the thermograms of both unmedicated and medicated MTDDS films.

Table 4. Thermal parameters of MTDDS films.

Light microscopy revealed the presence of spherical globules in the dried microreservoir films. The absence of drug crystals in the freshly dried films was in agreement with the DSC observations. Examples of microscopy for medicated MTDDS containing ASA and for the corresponding unmedicated MTDDS, as well as the corresponding globule size distribution are shown in Figure 3a. Globule size distributions of the non-aqueous emulsions and the resulting microreservoir films were monodispersed and skewed, with average globule sizes ranging from 3 to 6 µm. The biggest globule observed had a diameter of 30 µm. Examples of SEM pictures, with silicone mapping of silicone MTDDS containing IBU and K90 are shown in Figure 3b.

Figure 4 summarizes the stability data for the medicated microreservoir films, after 4-month storage. Some MTDDS at VP:drug molar ratio lower than 2:1 exhibited crystallization only at high humidity (‘crystallization at humid storage’) whereas some ratios crystallized at all storage conditions (‘crystallized’). All formulations were stable at 2:1 VP:drug molar ratio whereas at lower ratios physical stability decreased in the rank order from IBU, followed by SAA and ASA, indicating different activation energies and/or driving forces for crystallization of the free drug, and also differences in drug-polymer interaction propensities
as revealed via FTIR. Examples of microscopy showing impact of storage conditions are detailed in Figure 5 for silicone MTDDS containing SAA and K90.

Pure drugs and pure silicone adhesive had negligible water uptake compared to medicated and unmedicated silicone MTDDS (Figure 6a and Figure 6b). Unmedicated microreservoir systems absorbed more moisture than the medicated ones (p-values of 0.002 and 0.001 for MTDDS containing K12 and K90, respectively). If uptake of water is expressed in mole-% of total mole number N-vinylpyrrolidone (VP) units, water sorption isotherms become practically identical for all unmedicated films of different PVP loads, as expected. The reduced hydration of medicated films was in agreement with a drug-polymer interaction, which blocked binding sites for water. In drug loaded films, water absorption was reduced by a factor of 2 to 3 compared to unmedicated (PVP loaded) films, dependent on relative humidity (Figure 6b).

Considering that the silicone adhesive has a poor water uptake, the capacity of water absorption of the tested MTDDS was mainly determined by free hydrophilic groups in the microreservoirs. As illustrated in Figure 7, drug loading led to a comparable reduction of water absorption in IBU and ASA loaded films, with a reduced impact on hydration for K12 compared to K90. These observations may be explained by the similar solubility parameters of IBU and ASA and reduced drug mobility in microreservoirs containing K90 which has a higher molecular weight and Tg compared to K12. Such a kinetic effect in high molecular weight PVP grades was also observed for naproxen by Paudel et al\(^{37}\).

A slightly different impact of SAA on PVP hydration can be explained by the phenol group in this molecule which was available for hydrogen bonding, in addition to the carboxyl function. It has previously been reported that PVP has a high affinity to phenolic groups\(^{38-40}\) and that such interaction of SAA with PVP occurs via the carboxyl group as well as via the phenol-OH\(^{41}\).

Interestingly, drug loading decreased the relative amount of water absorption by 50% in all systems supporting the fact that a ratio of 2:1 or higher should lead to stable systems. The figures also indicate that K90 leads to stronger PVP/API interaction and should be consequently the superior stabilizer for IBU and ASA.
**Predictive Model**

It can be assumed that the observed reduction of water absorption in tested silicone MTDDS reflected the degree of PVP occupation by the drug. Considering a helix conformation of the PVP, the H-donor group of the drug can interact with two carbonyl groups of the PVP (via hydrogen bonding), as shown on Figure 8. The hydrogen atom can be reversibly shifted between two oxygen atoms. As a result, one of two carbonyl groups is blocked for water access, in agreement with results of Figure 7. A possible explanation of the deviation from the theoretical 2:1 VP:drug ratio (corresponding to a $F_{\text{inh}}$ of 50%) would be the steric hindrance exerted by the drug. The results of Figure 7 were obtained for films of VP:drug molar ratio of 2:1, consequently the reduction of water uptake by about 50% showed an apparent VP:drug ratio 1:1 upon hydration. An increase of humidity would indeed increase the chemical potential of the drug.

Figure 8 illustrates a possible reaction scheme for drug complexation in MTDDS, which considers results of DVS measurements and physical stability tests on formulations of different VP:drug ratios. Experimental data were in agreement with the fact that one hydrogen-bonding donor group of the drug (-COOH or -phenol-OH) interacts with two VP segments of PVP. This is consistent with postulated stoichiometry of hydrogen bonding for other HX-PVP complexes, such as the known iodine-PVP complex. Hydrogen bonds of the drug-VP complex I can be subject to a reversible fast shift of the hydrogen atom between two adjacent carboxamide groups, leaving one C=O group of two VP segments free for hydration. In addition, hydrophobic bonding of the alkyl chain has to be considered in such systems. The presence of free silanol groups in the silicone adhesive was mentioned by the manufacturer Dow Corning which can explain the complex formation via displacement of free silanol groups in our non-aqueous systems.

H-bonding with VP segments of PVP is possible via carboxylic or phenolic groups of the investigated candidates. R-OH: OH represents the OH of carboxyl function in ASA or IBU or the OH of the phenol group (SAA).

If VP:drug interaction occurs at a 2:1 molar ratio, only about 50% of carboxamide groups will be available for water binding in complex I as shown on Figure 8. Hydration of VP segments in unmedicated and medicated formulations can be described by schemes (a), (a’) and (b’) to illustrate that water absorption is reduced by approximately 50%. The equations furthermore demonstrate the impact of water activity on drug-polymer interactions; hydration
can occur in the transdermal system upon skin application and impacts on drug release due to
displacement of drug from PVP binding sites by water.

(a) **Hydration of VP-segments in drug-free systems:**

\[ n \text{ (VP)} + n \text{H}_2\text{O} \overset{\text{Fig. 6a}}{\rightleftharpoons} [\text{H}_2\text{O}...(\text{VP})]_n \overset{\text{Fig. 6b}}{\rightleftharpoons} [2\text{H}_2\text{O}...(\text{VP})]_n \overset{\text{Fig. 6c}}{\rightleftharpoons} [3\text{H}_2\text{O}...(\text{VP})]_n \]

Depending on the water activity, the molar water:VP ratio can reach \( \geq 3 \) (at high relative humidity)\(^{44,45}\). As shown in Figure 6b, approximately 300 mole-% of water (related to the total mole number of VP segments) were absorbed at 90% RH (water activity of 0.9).

**Hydration of VP-A complex** (A = active substance):

**Step 1 (a’): water activity < drug activity**

\[ n \text{H}_2\text{O} + m [A...(\text{VP})_2] \overset{\text{Fig. 6d}}{\rightleftharpoons} n [A...(\text{VP})_2...\text{H}_2\text{O}] + (m-n) [A...(\text{VP})_2] \]

**Step 2 (b’): water activity > drug activity**

\[ n \text{H}_2\text{O} + n [A...(\text{VP})_2...\text{H}_2\text{O}] \overset{\text{Fig. 6e}}{\rightleftharpoons} n \text{H}_2\text{O}...(\text{VP})_2...\text{H}_2\text{O} + nA \]

**Step 2 (b’)** of the above stoichiometric relationship explains dissociation of the drug (A) from the polymer, and thus the mechanism of drug release from the TDS matrix upon hydration when the patch is in contact with the skin.

In addition to above stoichiometric considerations, DVS measurements provided an estimate of a correction factor taking into account the reduction of the number of VP groups available for drug binding \( f_{VP}^{free} \) at different relative humidities, using (3), for a 1:1 molar interaction between water and VP unit. This ratio was consistent with DVS results on pure PVP, for a relative humidity lower than 60% (Figure 6). According to Wan et al.\(^ {45}\), about 3 molecules of water may be absorbed by one VP unit, at high relative humidity and this was supported by water sorption isotherms on unmedicated MTDDS.

\[
 f_{VP}^{free} (RH) = \frac{n_{VP}^{tot}}{n_{VP}^{tot} + n_{H_2O}(RH)}
\]
Where \( n_{VP}^{tot} \) is the total mole number of VP segments and \( n_{H_2O} \) is the mole number of water uptaken (obtained by DVS measurements on medicated MTDDS).

Figure 9 shows the linear relationship between apparent mole fraction of non-hydrated VP segments and the water activity, corresponding to the adjusted relative humidity. As soon as all free VP groups are occupied either by water or ROH, water will remove the drug from the PVP binding sites, at increasing activity. The different slopes of the regression lines for IBU and ASA, compared to SAA, may be indicative for an increased complex stability provided by the phenol group of SAA.

Figure 10 describes the different state of the drug when it is stabilized by hydrogen bonding with the PVP.

As we detailed previously for drug-in-acrylic systems\(^1\):

(4)

\[
K \approx \exp \left( \frac{\Delta G_v}{RT} \right)
\]

With

(5)

\[
K = \frac{X_F}{X_B} = \frac{n_F}{n_B}
\]

Where \( X_F \) and \( X_B \) are the mole fractions of free dissolved drug and of bound drug in the inner phase, respectively, and \( n_F \) and \( n_B \) are the respective mole numbers.

Also, for the partition of the drug between the PVP phase and the PSA phase, considering that the PSA and PVP are not miscible:

(6)

\[
n_{\text{drug}}^{\text{tot}} = n_{\text{drug}}^{\text{outer phase}} + n_{\text{drug}}^{\text{inner phase}}
\]

Where \( n_{\text{drug}}^{\text{tot}} \) is the total mole number of drug, \( n_{\text{drug}}^{\text{outer phase}} \) the mole number of drug in the adhesive phase and \( n_{\text{drug}}^{\text{inner phase}} \) the mole number of drug in the PVP phase.

The minimum amount of PVP required (\( n_{VP}^{min} \) or \( m_{VP}^{min} \) for the mass) to get a stable system can be then estimated (for a given drug load), for an interaction VP:drug 2:1 (\( \alpha = 2 \)) by assuming that all the VP units are available for binding with the drug (without taking into account the ambient humidity):

21
And consequently, 

\[
\frac{n_{VP}^{\text{min}}}{n_{\text{drug}}^{\text{tot}}} \approx \left(1 - \frac{\phi_1}{\omega_{\text{drug}}^{\text{tot}}}\right) \frac{2}{K + 1}
\]

With \(M_{VP}\) and \(M_{\text{drug}}\) the molecular weights of the VP unit and the drug, respectively and \(\phi_1\) the mass fraction of drug in the outer phase. Results for silicone MTDDS are summarized in Table 5.

**Table 5.** Experimental data and calculation results for medicated silicone MTDDS.

The free energy change upon crystallization increases from IBU, to SAA then ASA, i.e. the driving force for crystallization is highest for ASA. It is also worth noticing that \(K\) and \(\phi_1\) are estimates.

The impact of water uptake can also be taken into account. Indeed, upon hydration, some VP units will be occupied by the water and the molar quantity \(n_{VP}^{\text{free}}\) of VP units available for bonding with the drug is defined as:

\[
n_{VP}^{\text{free}} = \alpha f_{VP}^{\text{free}} n_{VP}^{\text{tot}}
\]

With \(n_{VP}^{\text{tot}}\) the total mole number of VP unit and \(f_{VP}^{\text{free}}\) a correction factor taking into account the reduction of the number of VP groups available for drug binding at different relative humidities, for a 1:1 molar interaction between water and VP unit (which is in agreement with experimental results on unmedicated films at low humidity). The stoichiometry of interaction between the drug and VP units is implied in the correction factor \(f_{VP}^{\text{free}}\). It reflects the fact that the probability for a drug:VP interaction is decreased by water uptake. It is calculated using the DVS measurements and equation (3).

So, from (7) and (9):
The value of \( f_{VP} \) was interpolated at 70% RH using the linear regressions shown above (Figure 9). Predicted values of minimum stable molar VP:drug ratio (using (10)), depending on humidity, were tabulated along with the experimental results of stability data in Table 6, for comparison. Theoretical values were in good agreement with experimental ones. The slight deviations observed in the case of IBU can be explained by the approximation made on the drug partition. This approach, based on DSC of pure drugs and DVS data of medicated (only VP:drug molar ratio 2:1) and unmedicated MTDDS films, offered a good estimation of the quantity of PVP required to prepare stable MTDDS films, taking into account the effect of hydration.

It is also useful to compare the Gibbs free energy change resulting from specific drug-polymer interactions with the Gibbs free energy changes resulting from the phase transition from the amorphous to the crystalline state of the drug at its pure state (\( \Delta G_v \)). Latter can be e.g. obtained by calculating Gibbs free energy change using the Hoffmann equation\(^{46}\).

The equilibrium constant calculated using Equation (4) concerned the conversion of bound drug to free amorphous drug. The system would be stable for:

\[
\Delta G_H = RT \ln K \leq \Delta G_v
\]

So

\[
RT \ln \frac{n_F}{n_B} \leq \Delta G_v
\]

From previous considerations, it can be deduced that:

\[
\frac{n_F}{n_B} = \left(1 - \frac{\phi_1}{\omega_{drug}}\right) \frac{1}{f_{free} f_{VP}} \frac{n_{VP}}{n_{drug}} - 1
\]

From (11), (12) and (13), the variation of \( \Delta G_H \) with humidity can be estimated.
A few data points, at low water activities (and for the whole range at a molar VP:drug ratio 2:1), directed to the formation of solid solutions, for which the calculated molar quantity of free drug was negative. This was in agreement with experimental results since these systems were physically stable and that a sufficiently high amount of drug was bound to VP segments at a molar 2:1 ratio. FTIR measurements on freshly prepared binary mixtures confirmed that hydrogen bonding played a key role for drug polymer interactions which blocked binding sites for water in microreservoir systems, as shown by DVS tests and discussed above. The differences between theoretical and experimental drug: PVP required ratios (Table 6) in the case of IBU can be explained by the fact that only an approximation of the drug partition between the inner and outer phases was used, which did not consider the impact of water uptake. Also, by using the theoretical drug solubility (determined using the limiting form of Flory-Huggins), it was assumed that the outer phase was saturated (i.e. the IBU concentration in the outer phase equaled its saturation solubility) but this does not take into account kinetic effects.

It is worth noticing that in the case of ASA, the physical stability of the MTDDS at higher water activities needed to be considered with care because of the potential hydrolysis of ASA to SAA, which could affect apparent physical stability of the formulation. Preliminary studies on the stability of ASA in silicone MTDDS containing K90 showed an increase in SAA content after 4 weeks. Further investigations would need to be carried out on the impact of chemical stability of ASA to confirm the evidence of ASA hydrolysis.

According to the experimental data, the application of the limiting form of the Flory-Huggins equation, in combination with the Hoffman equation, was very useful not only to estimate drug solubility but also to integrate the impact of water absorption on drug stability in described TDDS. Though a reduction in chemical drug potential may also be attributed to an entropy gain by drug-PVP mixing, the Gibbs free energy change caused by specific drug-polymer interactions can be regarded as the stability determining factor for the tested systems. In summary, our proposed thermodynamic approach (Equation 10) predicting physical stability of drugs in tested (semi-) solid dispersions and solutions at different water
activities, can be seen as a tool for an in-silico evaluation, planning of Design of Experiment (DoE) studies and the evaluation of drug release performance.

\[
\frac{n_{VP}^{tot}}{n_{drug}^{tot}} \approx \left(1 - \frac{\phi_1}{\omega_{drug}^{tot}}\right) \frac{1}{(K + 1)J_{VP}^{free}}
\]

CONCLUSION

Formulation of MTDDS containing amorphous drug-PVP (polymeric drug carrier) dispersions was shown to be feasible for the selected drug candidates (aromatic-based drugs that can interact via H-bonding) in silicone matrix and different PVP grades (high and low molecular weight).

Stable and crystal-free transdermal systems were manufactured at drug concentrations exceeding the drug solubility in the pure PSA, as the incorporation of PVP prevented the drug recrystallization, hence allowing an increased drug loading. The inner phase was a binary mixture of drug and PVP where specific drug-PVP interactions via hydrogen bonding were evidenced by FTIR. Moreover, DSC measurements confirmed drug-polymer miscibility as a unique T_g was detected for the binary mixtures. Water sorption isotherms were shown to be crucial for the evaluation of the drug activity at different drug-VP mixing ratios and relative humidity. To achieve target physical stability, drug and PVP concentrations have to be adjusted with respect to hydration effects on the amorphous solid dispersion in the silicone adhesive and the driving force of crystallization of the active ingredient. The estimated solubility data using our predictive thermodynamic approach may therefore be useful to define the design space for drug loading capacity of solid non-aqueous emulsions, or respectively microreservoir systems, intended for transdermal application. It considers the worst-case stabilization scenario as stabilization via kinetic effects, like stearic immobilization of the drug by the polymer, is not taken into account. In addition our proposed approach considers the impact of polymorphism on drug solubility and avoids the uncertainties of solubility parameter approach, which is based on data generated in silico using group additivity methods.
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DECLARATION OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Target structure of a MTDDS (schematic cross-section).

Figure 2. a) FTIR spectra of pure K90, pure IBU and binary mixtures (IBU, Kollidon 90F) with ratios VP:drug of 1:2, 1:1, 2:1, 3:1 and 4:1; b) FTIR spectra of pure silicone, pure IBU and IBU-in-silicone films.

Figure 3. a) Light microscopy of unmedicated (left) and medicated (right) microreservoir films containing K90 (4.9%) and ASA (4.9% K90 and 4% ASA) at a VP:drug molar ratio of 2:1 (lens ×100) b) SEM image of microreservoir film containing IBU and K90 at a VP:drug molar ratio of 2:1 (frame of 130 µm) with silicon mapping (in green).

Figure 4. Physical stability of microreservoir films at different storage conditions. “90” stands for K90 and “12” for K12.

Figure 5. Example of light microscopy of silicone MTDDS containing SAA and K90 after storage at ambient conditions and high humidity.

Figure 6. a) DVS results for medicated and unmedicated microreservoir films containing 5.3% PVP (K90) and IBU in comparison to DVS data of the pure drug and pure silicone adhesive (n=3). PVP isotherm is not shown because water uptake by pure PVP was much greater (around 60%(w/w) at 90% RH). Same trends were observed for SAA and ASA; b) DVS results for pure K90, and medicated and unmedicated silicone microreservoir films containing K90 (n=3). Same trends were observed using K12.

Figure 7. Inhibition of PVP hydration by drug-polymer interaction in silicone MTDDS ($F_{inh}$), with two different PVP grades (25°C) (n=3)
(a) MTDDS loaded with IBU and ASA
(b) MTDDS loaded with SAA.
**Figure 8.** Suggested reaction scheme for the drug-PVP complex formation and hydration effects in MTDDS containing aromatic acids.

**Figure 9.** Impact of water activity on the VP mole fraction available for complex formation in silicone MTDDS.

**Figure 10.** Scheme of drug stabilization via hydrogen bonding to get a solid drug solution (inner phase) in an adhesive matrix (outer phase).

$\Delta G_v$: the Gibbs free energy change for the drug phase transition between amorphous and crystalline

$\Delta G_{H}$: the Gibbs free energy change for hydrogen bonding

K: the equilibrium constant of specific drug-polymer interaction

**LEGEND FOR THE GRAPHICAL ABSTRACT**

Predicted value of minimum stable molar VP:drug ratio in microreservoir silicone films.