Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 67 (2007) 106–111
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Determination of ibuprofen solubility in wax: A comparison of microscopic, thermal and release rate techniques

Gbolahan Samuel Oladiran, Hannah Katharine Batchelor *

Medicines Research Unit, School of Life and Health Sciences, Aston University, Birmingham, United Kingdom

Received 4 August 2006; accepted in revised form 22 January 2007
Available online 27 January 2007

Abstract

The solubility of ibuprofen in Witepsol H15, a semi-solid wax matrix, was determined using microscopy, Higuchi release rates and HyperDSC (high speed differential scanning calorimetry); solubility values of 15–20%, 18.6% and 12.7% w/w resulted from the three techniques, respectively. Microscopy was useful in additionally examining crystal size, shape and homogeneity. Release rate experiments showed that release from these formulations followed Higuchi kinetics with an inflection in release rate constant at the drug loading corresponding to drug solubility. HyperDSC not only measured solubility but also determined the melting point of the formulation. The results from these three techniques correlated well, suggesting that the simpler techniques of microscopy or HyperDSC are appropriate to determine the solubility in semi-solid pharmaceutical formulations.

Keywords: HyperDSC; Ibuprofen; Witepsol; Solubility; Higuchi release rate

1. Introduction

Ibuprofen (2-(4-isobutylphenyl) propionic acid), a non-steroidal anti-inflammatory agent, is widely used in the treatment of pain and fever. Various pharmaceutical formulations of ibuprofen are available including oral tablets, suspensions, suppositories and transdermal gels and creams. Due to the very low aqueous solubility of ibuprofen, with a reported log *P* value of 3.51 [1], the bioavailability from such formulations is low [2,3]. Aqueous ibuprofen solubility is dependent on pH with increasing solubility with increased pH as described by Shaw et al. [4]. Recently Mills et al. [4] described the use of a wax-based transdermal product [5]; incorporating a poorly water soluble drug into a lipophilic carrier increased its solubility within the vehicle and thus improved the bioavailability from such a dosage form.

It is important to characterise the drug solubility within a transdermal delivery system to understand and predict the in vivo performance of the product. Higuchi postulated that the highest thermodynamic potential should be utilised to achieve the maximum efficacy, which usually corresponds to a saturated system [6]. Determination of drug solubility in semi-solids is problematic, therefore excess drug is added to produce a saturated system which is often wasteful and increases the cost of the formulation. Many methods have been used in attempts to measure solubility in semi-solids and these include microscopic examination [7]; conventional differential scanning calorimetry (DSC) [8,9]; HyperDSC [10]; infra-red attenuated total reflectance (IT-ATR) spectroscopy [11]; Higuchi release data [12] and X-ray powder diffraction (XRPD) [13]. Several methods were compared in measuring penciclovir solubility in films by Ahmed et al. [14], they found that visible microscopy was the simplest method to measure drug solubility although DSC, XRPD and release data provided additional information about release kinetics and drug characterisation.

Microscopy provides a simple method where the concentration at which crystals are first observed indicates

* Corresponding author. Medicines Research Unit, School of Life and Health Sciences, Aston University, Birmingham B4 7ET, United Kingdom. Tel.: +44 (0)121 204 3903; fax: +44 (0)121 359 2733.
E-mail address: h.k.batchelor@aston.ac.uk (H.K. Batchelor).

0939-6411/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2007.01.009

the upper limit of solubility of the drug in the vehicle. The use of differential scanning calorimetry (DSC) for the quantitative measurement of the solubility of drugs dispersed in semi-solid (polymeric) matrices was first described by Theeuwes et al. [9]. The DSC method was based on the simple principle that the fraction of drug solubilised within the matrix does not contribute to the melting endotherm associated with the dispersed drug fraction. Hence, by analysing a range of formulations having different concentrations of the drug and integrating the resultant peak seen in the thermogram within the region of the melting point of the drug, it is possible to calculate the heat of fusion (ΔH_f) associated with the thermal process. And, by plotting the measured ΔH_f values versus the drug concentrations for the range of formulations and extrapolating the resultant curve to the concentration axis, the solubility of the drug in the polymer was estimated. Victoria and David [15] analysed ethosuximide suppository formulations using DSC, they observed that at higher drug concentrations (>30% w/w) a separate endothermic melting peak was observed for the drug indicating that it was no longer soluble within the wax matrix, however they did not advance on this to determine the actual solubility of the drug within the wax.

HyperDSC, a variant form of conventional DSC, which has been used to determine solubility in semi-solids (silicones) was described by Gramaglia et al. [10]; the advantages of HyperDSC include the rapid scan rates (>200 °C per minute) that prevent kinetic events such as further dissolution of drug at elevated temperatures that are seen with slower scan rates of 10 °C per minute. This is of particular importance when looking at drug solubility in wax-based systems that are designed to melt at body temperature, where the melting temperature of the drug is much higher than that of the body. Also, working at very high scan rate, HyperDSC has the benefit of inhibiting any thermal events that contribute to further solubilisation as seen when conventional DSC methods were applied [10]. Furthermore, as a high throughput method (runs taking under 1 min compared to over 20 min for conventional DSC), it has been used for analysis of small sample mass with greater sensitivity [16]. Moreover, it has recently been demonstrated that HyperDSC is a better tool than conventional DSC in determination of drug solubility within semi-solids [17].

Higuchi [18] reported on the release kinetics of drugs from ointment bases when the drug was loaded at different concentrations. It was found that there was a linear relationship between the amount of drug released and the square root of time depending on the state (either dissolved or dispersed) of the drug within the matrix provided that the drug was homogeneously distributed and its loading concentration was much greater than its solubility within the matrix and as long as sink conditions applied.

Mathematically this is represented in the following equations:

$$\text{For a suspension } Q = [D(2A - C_s)C_s t]^{1/2} \quad (1)$$

$$\text{For a solution } Q = 2A\left(\frac{Dt}{\pi}\right)^{\frac{1}{2}} \quad (2)$$

where Q is the amount of drug released after time, t per unit exposed area, D is the diffusivity of the drug within the matrix, A is the initial total drug concentration and C_s is the drug solubility within the matrix. Both equations describe drug release as being linear with the square root of time:

$$Q = k_H t^{1/2} \quad (3)$$

where k_H is the release rate constant, the slope of a plot of Q versus $t^{1/2}$; although this value differs according to whether the drug is in suspension or solution. A plot of k_H versus concentration will have an inflection at the point where the drug is no longer soluble but suspended within the matrix and thus offers a means of measuring drug solubility.

The objective of this work was to investigate the suitability of microscopy, HyperDSC and release experiments for determining ibuprofen solubility in wax matrices. The solubility values for each of the methods were compared and the limitations or benefits of each technique were considered.

2. Materials and methods

2.1. Materials

Ibuprofen, acetonitrile, phosphate buffer tablets and orthophosphoric acid were bought from Fischer Chemicals, UK. Witepsol H15 was a gift from Sasol, Germany.

2.2. Methods

2.2.1. Preparation of wax based tablets

Formulated matrices were made using low temperature conventional tableting technology as described by Mills [4]. This method enabled reproducible drug content of each formulated batch. Weighed drug was dispersed gently into the melted wax at approximately 45 °C and this was continuously stirred until completely homogeneous before being allowed to set via cooling. It was then crushed into granules using a mortar and pestle; these granules were stored at −20 °C overnight and further milled using a mortar and pestle to form a coarse powder (particles of approximately 1 mm diameter). Small tablets were prepared; 100 mg of the powder was subjected to two tonnes force for 10 s on Specac (series 15.011; UK) conventional KBr press to make cylindrical tablets of 5 mm diameter. Tablets made were stored at 4 °C until needed. Formulations were prepared using Witepsol and ibuprofen at the following concentrations of ibuprofen; 1%, 2%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40% and 50% w/w drug loading.

2.2.2. Uniformity in weight

European Pharmacopoeia method 2.9.5 was used to determine the uniformity of weight of the formulated

tablets, no more than two tablets should deviate by 7.5% of the mean weight and no tablet should deviate by more than 15% of the mean weight. 20 tablets were randomly selected and weighed individually using a four decimal place Kern 770 balance (Kern, Germany).

2.2.3. Microscopy

Blends of ibuprofen and Witepsol at each concentration were examined under a microscope with a 4× objective lens for the presence of ibuprofen crystals and photographs taken with an Axio high resolution camera. Images were captured using Axiovision version 3.1 software.

2.2.4. UV-HPLC method

Analysis was carried out on an agilent 1100 series chromatography system. 100 μl of each sample was injected into the thermo Hypersil ODS column (150 × 4.6) mm and the drug was eluted by a pre-filtered and degassed isocratic mobile phase system consisting of acetonitrile: double distilled water: orthophosphoric acid (50:50:1) at a flow rate of 1 ml/min. The agilent variable detector used was set at 225 nm. A calibration showed that the peak area was linearly related ($r^2 = 0.999$) over the concentration range 1–100 μg/ml.

2.2.5. In vitro drug release

The release study was carried out using the USP II basket type method using 200 ml of phosphate buffered saline (PBS) at pH 7.4 as dissolution medium (maintained at 33 ± 1 °C); one ibuprofen loaded wax tablet was placed in each basket and rotated at 100 rpm. pH 7.4 was used for this study as the aqueous solubility of ibuprofen is pH dependent and this pH ensures sink conditions are maintained throughout. Samples were collected at designated intervals (and replaced with fresh medium) and analysed via UV-HPLC. Release data were plotted according to Eq. (3) and the release rate constant was calculated for each drug loading. The solubility was determined as the inflection from a plot of k_H versus drug loading.

2.2.6. HyperDSC experimental protocol

The thermal analysis was carried out in a pre-calibrated (for temperature and enthalpy at 500 °C/min using an indium standard; Perkin-Elmer) Diamond DSC (Perkin-Elmer, Pyris series 5.0). 1.90 ± 0.05 mg of formulated coarse powder (as described in Section 2.2.1) was placed air tight in hermetically sealed aluminium pans suitable for volatile materials (Perkin-Elmer) and analysis was carried out within the temperature range (−30 to 200 °C). Moisture-free helium was used as the purge gas at a flow rate of 20 mL/min, an empty pan was used as a reference for each run. The resulting thermogram was analysed using Pyris series 5 data software (Perkin-Elmer) and the area under the phase transition endotherm; heat of fusion ; ΔH_f was manually integrated and recorded. Reproducible results have previously been achieved under these conditions [10,17]. Drug solubility was determined from the intercept of a plot of enthalpy of fusion (J/g) versus drug loading (% w/w).

3. Results and discussion

3.1. Uniformity of weight

European Pharmacopoeial method 2.9.5 was used to determine the uniformity of weight of the formulated tablets, all tablets were within 2.0% of the mean tablet mass.

3.2. Microscopy

Ibuprofen loaded Witepsol was observed under a microscope at loadings of 1%, 5%, 10%, 15%, 20%, 25% and 30% w/w. Solid crystals were first observed in the 20% loaded ibuprofen with no solid material being observed at 10% or 15% w/w. As the loading increased greater numbers of solid crystals were observed (Fig. 1). This suggested that the solubility of ibuprofen is between 15% and 20% w/w.

3.3. In vitro drug release

Drug release from the matrices followed Higuchi kinetics with a plot of cumulative amount released versus square root of time being linear ($R^2 > 0.95$ in all cases). The release rate constant, k_H, obtained from the slope of the Higuchi plots increased as the drug concentration in the matrices increased from 1% to 35% (w/w) (Fig. 2). This

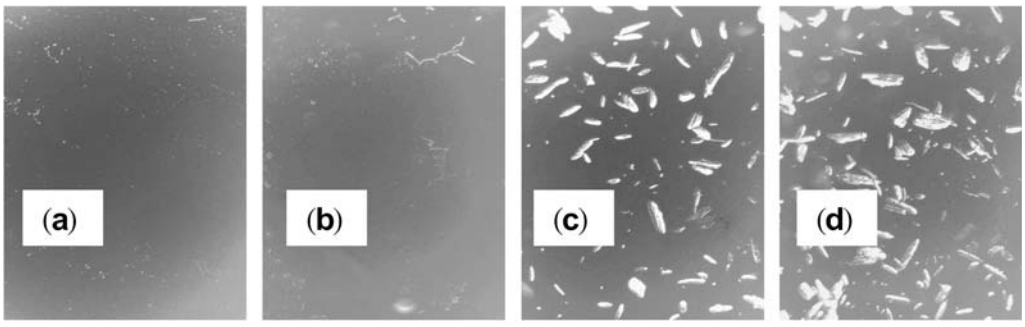

Fig. 1. Microscopy images of (a) Witepsol alone; (b) Witepsol plus ibuprofen at 15% w/w loading, (c) Witepsol plus ibuprofen at 20% w/w loading and (d) Witepsol plus ibuprofen at 25% w/w loading. All images were taken at 4× magnification.

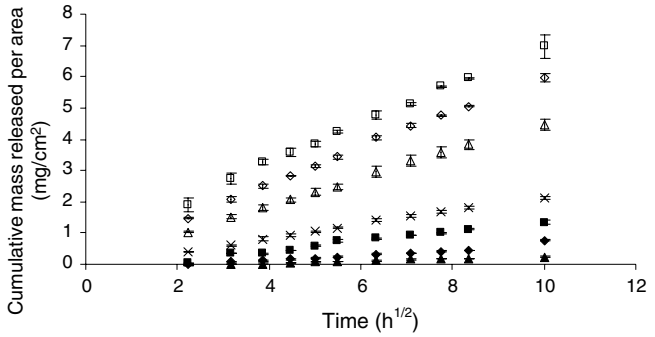

Fig. 2. Higuchi square root of time plots for ibuprofen release from wax matrices at (▲) 1% w/w, (◆) 2% w/w, (■) 5% w/w, (×) 7.5% w/w, (△) 25% w/w, (◇) 25% w/w and (□) 30% w/w ibuprofen loading. Data show means ± standard deviation.

was expected as the leaving potential of the drug is enhanced with increasing drug loading concentration; hence the boost in the force that drives the release process. Furthermore, the drug molecules remain evenly distributed within the matrix as loading concentration increases up to saturation beyond which a larger proportion will be suspended within the matrix.

When the drug is soluble within the wax matrix (in solid-solution) large increases in release rate constant are expected as the concentration gradient between the formulation and surrounding medium is high. When excess drug is present and the formulation is saturated the increase in release rate constant is lower as the concentration gradient was at a maximum and drug has to dissolute to maintain the concentration gradient. Therefore, a plot of k_H against loading showed two distinct linear relationships (Fig. 3).

Linear regression analysis of data for the drug dissolved in the wax gave a straight line, $r^2 = 0.99$ and regression of data for the drug suspended in the wax (when excess drug was present) also gave a straight line, $r^2 = 0.92$. Intersection of the two extrapolated lines provides an estimation of drug solubility, the value calculated from Fig. 3 above was 18.6% w/w. The error associated with this technique was calculated based on the maximum and minimum deviations associated with the standard deviations; best fit lines were drawn for each data set (mean either plus or minus the standard deviation) and the intersections were determined providing the range for solubility prediction to be 18.5–19.0% w/w.

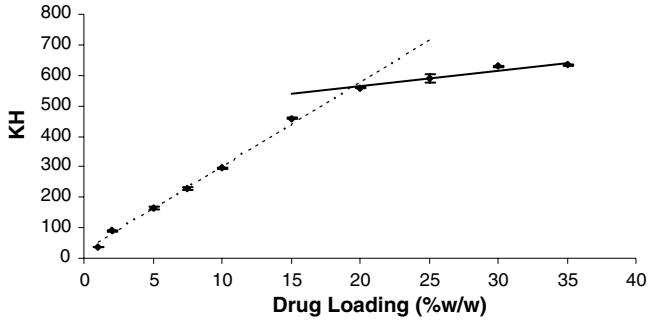

Fig. 3. A plot of release rate constant, k_H versus drug loading, drug dissolved in wax with dashed line extrapolation of best fit line, drug suspended in wax with solid line extrapolation of best fit line. Data show means ± standard deviation.

3.4. HyperDSC

Ibuprofen gave a sharp single endothermic peak at 75 °C and enthalpy of fusion of 152 ± 2 J/g (Fig. 4), this represents the melting temperature of ibuprofen [1]. This corresponds well to previous studies that showed the enthalpy of fusion of ibuprofen to be 150 J/g [19]. Witepsol H15 alone showed a single well-defined endothermic peak with an onset of 33 °C (Fig. 4). This corresponds to the reported melting point of Witepsol H15 [20].

Broad endotherms were observed for all formulations between 30 and 45 °C corresponding to the melting of the wax (Fig. 5). However, as ibuprofen concentration increased to 30% w/w, another smaller endothermic peak with the onset at 68 ± 1 °C was observed which became more prominent as the drug concentration increased to 50% w/w ibuprofen loading (Fig. 5). This second peak related to dispersed drug within the formulation as it occurred at the melting temperature of ibuprofen. Fig. 5 shows the effect of increasing the drug loading concentrations from 30% to 50% (w/w). Further, it indicated a decrease in the observed onset of the drug (68 ± 1 °C) compared to that calculated when pure ibuprofen alone was analysed (74 ± 1 °C). This decrease is likely due to the dissociation

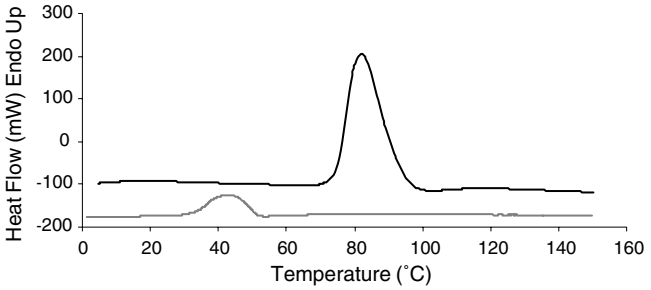

Fig. 4. Hyper differential scanning calorimetry thermograms of pure ibuprofen (upper black line) and pure Witepsol H15 (lower grey line).

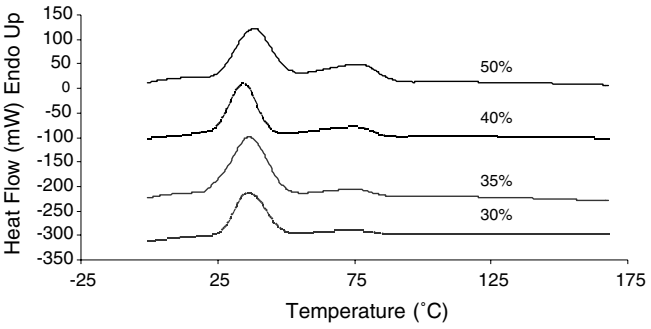

Fig. 5. Hyper differential scanning calorimetry thermograms of ibuprofen loaded wax matrices at increasing drug loadings.

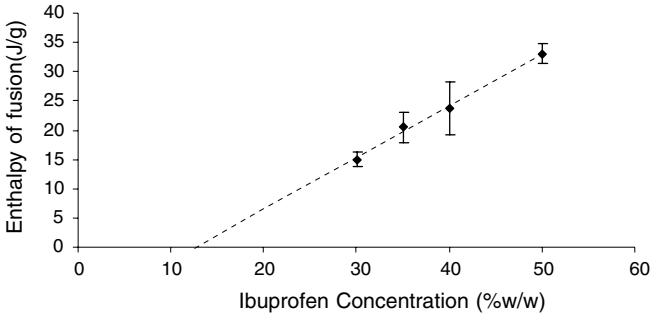

Fig. 6. A plot of enthalpy of fusion versus ibuprofen loading, the extrapolated line intersects the x-axis at the solubility of drug in the wax. Data show means ± standard deviation.

effect caused by the applied melting method used during the formulation process as well as the distribution effect of the drug molecules within the matrix, as reported previously [10]. Furthermore, the onset melting point of the base was also lowered from 33 ± 1 °C to around 25 ± 1 °C; thus the formulation can easily melt at body temperature. This was expected as it was reported in the literature that fat soluble medication such as chloral hydrate depressed the melting point of wax base [21]. However, this is contrary to the result reported when indomethacin was added to Witepsol H-15 where an increase in melting temperature was observed [22]. Furthermore, increasing the loading drug concentration did not have any significant effect on the hardening behaviour of the base but noticeably, the time taken for the formulation to set after mixing prior to crushing into granules increased with drug loading. At the concentration when the drug was noted (via macroscopic observation) to be soluble in the matrix, the formulation takes longer to set than when the drug was also dispersed. This is likely to be due to the interaction between the molten matrix (solvent) and the drug molecules. At lower drug loadings, the drug molecules break away from their crystals and are inserted into the 'solubilising cavity' of the molten matrix thereby disrupting the bond between the molecules of the matrix. But at higher drug loading; when drug is dispersed, more molecular drug interactions enhance formation of a more stable and organised crystal structure to outweigh the solubilising effect seen when drug molecules are completely soluble in the molten matrix, with drug crystals acting as seeds to promote wax-hardening.

According to the concept first described by Theeuwes et al. [9] that thermodynamic effects (represented by endothermic peaks at the melting temperature of the drug) seen during thermal analysis of a drug in a matrix from the undissolved and/or dispersed part of a drug [8]. The heat of fusion; ΔH_f; taken as the area under the endothermic peak for the melting of ibuprofen was plotted against the various concentrations of the drug loading in the matrix (Fig. 6). Extrapolation of the mean data to the x-axis gave an estimate of the drug solubility within the matrix. The solubility value of ibuprofen in the wax matrix as calculated by this method was 12.7% w/w. The error associated with this method was calculated using the standard deviations to produce a data set of positive and negative deviations and following the procedure as with the mean values; the solubility range was determined to be 10.4–15.0% w/w. Fig. 6 shows the plot of the mean values with standard deviations and the line of best fit through the mean data set with a regression value of 0.995.

4. Conclusions

The solubility of ibuprofen in a wax matrix was measured using three techniques. Visible microscopy was a simple technique that demonstrated the solubility to be between 15% and 20% w/w. Microscopy offered an uncomplicated technique that provided qualitative data on the solubility of a drug in a semi-solid and also demonstrated the homogeneity of drug distribution within the wax matrix. The release studies suggested the solubility of ibuprofen was 18.6% w/w; this concurs with the value found using microscopy and provided quantitative data according to theoretical models. Release experiments are time-consuming to perform and require additional analysis via HPLC (or a similar analytical technique to measure drug concentration) and also mathematical manipulation of the data. In addition, data gathered from concentrations distant to the region of interest are most useful in determining the solubility within a semi-solid. The advantage of release experiments is that they also provide interesting information about the release properties of the drug from the formulation that is of importance in formulation design. HyperDSC analysis suggested that the solubility of ibuprofen in Witepsol H15 was 12.7% w/w, this value is somewhat lower than the values suggested by microscopy and release studies. HyperDSC as an analytical tool is rapid and requires very small sample sizes (less than 2 mg); the data are quantitative and provide a good estimation of drug solubility within semi-solids. Furthermore, HyperDSC provides additional information on interactions that may occur between the drug and excipients present within a formulation.

References

[1] J. Hadgraft, J.D. Plessis, C. Goosen, The selection of non-steroidal anti-inflammatory agents for dermal delivery, Int. J. Pharm. 207 (2000) 31–37.
[2] M.K. Ghorab, M.C. Adeyeye, Enhancement of ibuprofen dissolution via wet granulation with beta-cyclodextrin, Pharm. Dev. Technol. 6 (2001) 305–314.
[3] F.K. Glowka, Stereoselective pharmacokinetics of ibuprofen and its lysinate from suppositories in rabbits, Int. J. Pharm. 199 (2000) 159–166.
[4] L.R. Shaw, W.J. Irwin, T.J. Grattan, B.R. Conway, The effect of selected water-soluble excipients on the dissolution of paracetamol and ibuprofen, Drug Dev. Ind. Pharm. 31 (2005) 515–525.
[5] S. Mills, J. Staniforth, M. Tobyn, Metered dose dermal drug delivery: Pandermal™ tablets, AAPS PharmSci. 3 (2001) 3.
[6] T. Higuchi, Physical chemical analysis of percutaneous absorption processes from creams and ointments, J. Soc. Cosmetic. Chem. 11 (1960) 85–97.

[7] A. Gopferich, G. Lee, Determining the solubility and crystal form of clenbuterol in thin films of Eudragit NE30D, Drug Dev. Ind. Pharm. 18 (1992) 319–331.
[8] M.R. Jenquin, J.W. McGinity, Characterization of acrylic resin matrix films and mechanisms of drug–polymer interactions, Int. J. Pharm. 101 (1994) 23–34.
[9] F. Theeuwes, A. Hussain, T. Higuchi, Quantitative analytical method for determination of drugs dispersed in polymers using differential scanning calorimetry, J. Pharm. Sci. 63 (1974) 427–429.
[10] D. Gramaglia, B.R. Conway, V.L. Kett, R.K. Malcolm, H.K. Batchelor, High speed DSC (HyperDSC) as a tool to measure the solubility of a drug within a solid or semi-solid matrix, Int. J. Pharm. 301 (2005) 1–5.
[11] A.S. Cantor, Drug and excipient diffusion and solubility in acrylate adhesives measured by infrared-attenuated total reflectance (IR-ATR) spectroscopy, J. Control Release 61 (1999) 219–231.
[12] Z.T. Chowhan, R. Pritchard, Release of corticoids from oleaginous ointment bases containing drug in suspension, J. Pharm. Sci. 64 (1975) 754–759.
[13] R. Suryanarayanan, S. Venkatesh, L. Hodgin, P. Hanson, Determination of the physical state of salicylic acid in hydrogel formulations by X-ray diffractometry, Int. J. Pharm. 78 (1992) 77–83.
[14] A. Ahmed, B.W. Barry, A.C. Williams, A.F. Davis, Penciclovir solubility in Eudragit films: a comparison of X-ray, thermal, microscopic and release rate techniques, J. Pharm. Biomed. Anal. 34 (2004) 945–956.
[15] M.M. Victoria, C.J. David, Thermal and rheological study of lipophilic ethosuximide suppositories, Eur. J. Pharm. Sci. 19 (2003) 123–128.
[16] P. Gabbott, P. Clarke, T. Mann, P. Royall, S. Shergill, A high-sensitivity, high-speed DSC technique: measurement of amorphous lactose, American Laboratory 35 (2003) 17–22.
[17] M. Saunders, K. Podluii, S. Shergill, G. Buckton, P. Royall, The potential of high speed DSC (Hyper-DSC) for the detection and quantification of small amounts of amorphous content in predominantly crystalline samples, Int. J. Pharm. 274 (2004) 35–40.
[18] T. Higuchi, Rate of release of medicaments from ointment bases containing drugs in suspension, J. Pharm. Sci. 50 (1961) 874–875.
[19] M. Manish, J. Harshal, P. Anant, Melt sonocrystallization of ibuprofen: effect on crystal properties, Eur. J. Pharm. Sci. 25 (2005) 41–48.
[20] T. Takatori, N. Shimono, K. Higaki, T. Kimura, Evaluation of sustained release suppositories prepared with fatty base including solid fats with high melting points, Int. J. Pharm. 278 (2004) 275–282.
[21] R.C. Rowe, P.J. Sheskey, P.J. Weller, The Handbook of Pharmaceutical Excipients, Pharmaceutical Press, London, 2005.
[22] C. De Muynck, J.P. Remon, Influence of fat composition on the melting behaviour and on the in vitro release of indomethacin suppositories, Int. J. Pharm. 85 (1992) 103–112.