Hydrogen Bonding with Adsorbent during Storage Governs Drug Dissolution from Solid-Dispersion Granules

Manish K. Gupta,[1] Yin-Chao Tseng,[2] David Goldman,[2] and Robin H. Bogner[1, 3, 4]

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Purpose. To investigate changes in drug dissolution on storage of ternary solid-dispersion granules containing poorly water-soluble drugs.

Methods. Hot-melt granulation was used to prepare ternary solid-dispersion granules in which the drug was dispersed in a carrier and coated onto an adsorbent. Seven drugs including four carboxylic acid-containing drugs (BAY 12-9566, naproxen, ketoprofen, and indomethacin), a hydroxyl-containing drug (testosterone), an amide-containing drug (phenacetin), and a drug with no proton-donating group (progesterone) were studied. Gelucire 50/13 and polyethylene glycol (PEG) 8000 were used as dispersion carriers whereas Neusilin US2 (magnesium aluminosilicate) was used as the surface adsorbent.

Results. Two competing mechanisms have been proposed to explain the complex changes observed in drug dissolution upon storage of solid dispersion granules. Conversion of the crystalline drug to the amorphous hydrogen bonded (to Neusilin) state seems to increase dissolution, whereas, the phenomenon of Ostwald ripening can be used to explain the decrease in drug dissolution upon storage. The solubility of the drug in Gelucire is a crucial factor in determining the predominant mechanism by governing the flux toward the surface of Neusilin. The mobility for this phenomenon was provided by the existence of the eutectic mixture in the molten liquid state during storage.

Conclusions. A competitive balance between hydrogen bonding of the drugs with Neusilin and Ostwald ripening determines drug dissolution from solid-dispersion granules upon storage.

KEY WORDS: solid dispersion; dissolution; hydrogen bonding; crystallinity; stability.

INTRODUCTION

There is renewed interest in the formulation of solid dispersions as a promising approach to enhance the dissolution of poorly water-soluble drugs (1–4). However, the key limitations to their widespread commercial use include problems in processing solid dispersions into dosage forms and reversion of the amorphous drug to the lower energy crystalline state on storage (3,4). Reversion to the lower energy crystalline state from the non-equilibrium higher energy amorphous state leads to a decrease in drug dissolution, thereby, defeating the very purpose of formulating solid dispersions. As discussed in the reviews by Serajuddin and by Leuner and Dressman (3,4), physical stability of the drugs in solid dispersions seems to be the rate-limiting step in using this approach to enhance dissolution and oral bioavailability of poorly water-soluble drugs.

In previous work a combination of solid dispersion and surface adsorption was used to prepare ternary solid-dispersion granules, with enhanced drug dissolution and feasibility of compression into tablets (5). The dissolution of a poorly water-soluble drug, BAY 12-9566, was enhanced by dispersing it in Gelucire 50/13 and coating the dispersion on Neusilin US2 using hot-melt granulation (5). Interestingly it was found that drug dissolution from the granules was further enhanced on storage at 40°C/ 75% RH for 4 weeks. This result is in sharp contrast to the more general phenomenon of reduced dissolution on storage resulting from reversion to the crystalline state. An increase or a decrease in drug dissolution on storage of a formulation is not acceptable from a stability standpoint and mandates further investigation for the development of a stable robust formulation.

In a follow-up study it was shown that hydrogen bonding between several drugs and the adsorbent, Neusilin was key to the further enhancement of drug dissolution on storage of granules (6). On storage, a decrease in drug crystallinity (from X-ray powder diffractometry) and a corresponding increase in the drug hydrogen-bonded to Neusilin (from Fourier transform infrared spectroscopy) were observed for both BAY 12-9566 and naproxen granules but not for progesterone granules (6).

Under the storage conditions (40°C/ 75% RH) used previously (5,6), relatively high mobility in the eutectic melt of the solid-dispersion was expected to allow nucleation and reversion of the drug to the crystalline state leading to decreased drug dissolution upon storage. However, in the presence of another amorphous phase, Neusilin, there was the potential for the drugs to diffuse toward the surface of the adsorbent. We proposed that Neusilin hydrogen bonded with drugs (such as BAY 12-9566 and naproxen), thereby preventing their reversion from the amorphous to crystalline state (6). Neusilin (magnesium aluminosilicate) has silanol groups on its surface that make it a potential proton donor as well as an acceptor. The hydrogen bonding potential of silanols in the local environment on silica surfaces is well-documented (7,8). In a recent study the hydrogen-bonding interaction between silanol groups in colloidal silicon dioxide and indomethacin (a carboxylic acid containing drug) was revealed using ^{29}Si and ^{13}C solid-state nuclear magnetic resonance studies (9). Thus, hydrogen bonding between the drugs under investigation (with proton accepting and/ or donating potential) and Neusilin is possible. In contrast to a previous report that addresses the prevention of reversion of the amorphous state of a drug (indomethacin) due to hydrogen bonding with a carrier (polyvinyl pyrrolidone) in a single phase system (10), we found evidence for formation of additional hydrogen bonds of the drug onto a phase separated amorphous interface on storage.

This study was designed to test the generalizability of the proposed mechanism using seven drugs, two solid dispersion carriers, and an adsorbent. The drugs include four carboxylic acid containing drugs (BAY 12-9566, naproxen, ketoprofen,

[1] School of Pharmacy, University of Connecticut, Storrs, Connecticut 06269

[2] Pharmaceutical Technology, Pharmaceutical Division, Bayer Corporation, West Haven, Connecticut 06269

[3] Institute of Materials Science, University of Connecticut, Storrs, Connecticut 06269

[4] To whom correspondence should be addressed at University of Connecticut, U-2092, Storrs, Connecticut 06269. (e-mail: BOGNER@UCONNVM.UCONN.EDU)

and indomethacin), a hydroxyl containing drug (testosterone), an amide containing drug (phenacetin), and a drug with no proton-donating group (progesterone) were studied. These poorly water-soluble drugs were chosen to have a range of functional groups having potential to hydrogen bond with Neusilin so as to investigate the generalizability of the proposed mechanism. Gelucire 50/13 (melting range: 47–53°C) and PEG 8000 (melting range: 60–63°C) have been used in solid dispersion formulations and make good choices for low melting solid dispersion carriers (11–14). Neusilin US2 has a high specific surface area (~300 m^2/g) and consists of amorphous microporous granules with potential for hydrogen bonding (15). Neusilin US2 was, therefore, used as the adsorbent.

The physical properties of solid dispersions can be studied using techniques such as Fourier transform infrared spectroscopy (FT-IR), X-ray powder diffraction (XPD), and modulated differential scanning calorimetry (MDSC) (16–20). Hydrogen bonding between drugs and excipients was investigated using FT-IR spectroscopy. XPD was used to examine the crystallinity of drugs in the dispersion granules. MDSC was performed to determine the melting point of the eutectic mixture of the drug and dispersion carrier in the dispersion granules. Solubility of the drugs in the dispersion carrier was estimated gravimetrically in a temperature controlled UV spectrophotometer. Ternary solid-dispersion granules of the seven drugs were prepared by hot-melt granulation. Drug dissolution from the initial granules (upon formulation) was compared with that after storage at 40°C/ 75% RH for 2 and 4 weeks. FT-IR, XPD, MDSC, and solubility data were used to explore underlying mechanisms resulting in changes in the dissolution profiles upon storage. The generalizability of the previously proposed mechanism was thereby tested.

MATERIALS AND METHODS

Experimental

All the seven drugs were poorly water-soluble, thermostable compounds with different hydrogen bonding potential. The four carboxylic acid-containing drugs include BAY 12-9566, naproxen, ketoprofen, and indomethacin. BAY 12-9566 has a melting point of 110°C. Naproxen USP, ketoprofen USP, and indomethacin USP have melting points of 152°C, 94°C, and 162°C, respectively, and were obtained from PCCA (Houston, TX). The amide-containing phenacetin (purified powder) and hydroxyl-containing testosterone USP, have melting points of 135°C and 155°C, respectively, and were obtained from PCCA (Houston, TX). Progesterone USP (α-form), with no proton-donating group, has a melting point of 130°C and was obtained from Sigma (St. Louis, MO). The structures of these seven drugs are shown as Fig. 1. Gelucire 50/13, a polyglycolized glyceride, was used as received from Gattefosse (Westwood, NJ). Gelucire 50/13 is obtained from hydrogenated vegetable oils consisting of mono-, di-, and triglycerides and mono- and di-fatty acid esters of PEG 1500. Polyethylene glycol 8000 (PEG 8000, Carbowax, Sentry grade) was obtained from Union Carbide (Danbury, CT). Fuji Chemicals (Englewood, NJ) supplied magnesium aluminosilicate (Neusilin US2). A laboratory scale low shear granulator (Mini MGT, L. B. Bohle Incorporated, Bristol, PA), fitted with a heating jacket, was used to prepare granules.

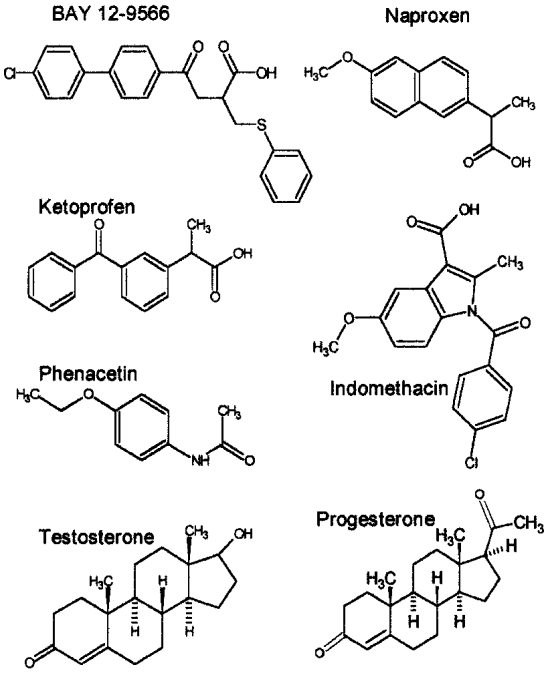

Fig. 1. Structures of the seven drugs.

Formulation of Solid-Dispersion Granules

Ternary solid-dispersion granules were prepared using hot melt granulation. The details of preparation were described earlier (5). Briefly, the drug was added into the molten dispersion carrier and heated to obtain a clear molten mixture. Neusilin US2 was preheated to 80°C in the granulator with stirring at 300 rpm. The molten mixture was then added dropwise over a period of one minute to Neusilin with continued stirring. Hot melt granulation was performed at an increased stirring speed of 600 rpm for one more minute to obtain ternary solid-dispersion granules of each of the drugs, dispersion carrier and adsorbent in a ratio of 1:1:1. The ternary dispersion granules of the seven drugs were prepared with Gelucire 50/13 as the dispersion carrier and Neusilin as the adsorbent. Ternary dispersion granules of BAY 12-9566, naproxen, and progesterone were also prepared using PEG 8000 in place of Gelucire 50/13. The granules were sieved through mesh # 18 BSS. The abbreviations used to describe the components of these solid-dispersion granules are included in parentheses: BAY 12-9566 (Bay), naproxen (Nap), ketoprofen (Ket), indomethacin (Ind), phenacetin (Phe), testosterone (Tes), progesterone (Pro), Gelucire 50/13 (G), PEG 8000 (P), and Neusilin US2 (N). For example ternary granules containing BAY 12-9566, Gelucire 50/13 and Neusilin US2 would be represented as Bay/G/N.

Preparation of Amorphous State of Drugs

The amorphous state of each of the seven drugs was prepared by melting followed by quench cooling in liquid nitrogen. The amorphous nature of these drugs was ensured by absence of birefringence under cross-polarized light.

Dissolution Testing

Dissolution profiles of the drugs from their solid-dispersion granules were determined using a USP Type II apparatus at 50 rpm. The dissolution medium consisted of 0.1 N HCl with sodium lauryl sulfate (SLS) for all the drugs other than phenacetin, where 0.05 M, pH 7.0 phosphate buffer was used. All the drugs were, thereby, maintained in the unionized state in the dissolution medium. Dissolution profiles in the previous study were determined using 30-mg dose of BAY 12-9566 (5). This dose corresponds to 17% of saturation solubility at 37°C in 900 ml of 0.1 N HCl and 1% w/v SLS. Based on the equilibrium solubility values, 25 mg doses of naproxen, 70 mg of ketoprofen, 70 mg of indomethacin, 25 mg of testosterone, and 25 mg of progesterone required 0.25%, 0.25%, 1%, 0.1%, and 0.1% w/v SLS, respectively in 0.1 N HCl to maintain similar sink conditions in the dissolution medium (~17% of saturation solubility). For phenacetin, 175-mg dose was used in 0.05M, pH 7.0 phosphate buffer to maintain similar sink conditions and the unionized state of the drug. Dissolution samples were analyzed for drug concentration from the absorbance values at the respective wavelength of peak absorbance.

Examination of Hydrogen Bonding

FT-IR spectra were measured using a spectrometer (Model Magna IR 560, Nicolet Instrument Technologies Inc., Madison, WI). KBr pellets of each drug alone as well as solid-dispersion granules were prepared. An average of 100 scans of each sample was collected at 4 cm^{-1} resolution over a wavenumber region of 4000–600 cm^{-1}. FT-IR spectra of pure crystalline as well as pure amorphous state of drugs were measured for comparison with the spectra of the granules.

Evaluation of Crystallinity

Samples of each drug in its pure crystalline state and formulated as solid-dispersion granules were studied for crystallinity using a diffractometer (Model D5005, Bruker AXS Inc., Madison, WI) using Cu$K\alpha$ radiation, a voltage of 40kV, and a current of 40mA. The scanning rate was 1.25°/min over a 2θ range of 5–50° with a sampling interval of 0.02°.

Storage of Solid-Dispersion Granules

Solid-dispersion granules were stored at 40°C/ 75% RH for 4 weeks. Their dissolution profiles were determined after storage and compared to those of the initial granules. FT-IR spectra of the initial and stored granules were compared to examine changes in hydrogen bonding of drugs, if any. X-ray powder diffractograms of the initial and stored granules were compared to evaluate any changes in drug crystallinity.

Determination of the Melting Point of the Eutectic Mixture

The temperature for the onset of melting of the eutectic mixture in the solid dispersion granules was determined using a modulated DSC instrument (Model 2920, TA Instruments). The instrument was calibrated in the modulated mode using high purity indium with helium as the purge gas. The dispersion granules (~4 mg) were hermetically sealed in aluminum sample pans (Perkin–Elmer, Norwalk, CT, USA). A modulated temperature program with a period of 60 s, an amplitude of ±0.4°C, and an overall heating rate of 2°C/ min was used from –40°C to a temperature above the melting point (T_m + 10°C) of the drug.

Estimation of Solubility of Drugs in the Dispersion Carriers

The solubilities of the seven drugs were determined in the dispersion carriers using a temperature controlled UV spectrophotometer (Model Cary 50 Bio, Varian Instruments). The dispersion carrier (2 g) was allowed to melt in the cuvette at 60°C, which is well above the melting point of the dispersion carrier. Accurately weighed increments of the drug (5 mg at a time) were then added to the cuvette followed by the stirring of the sample using a magnetic stirrer. Upon addition of drug to the cuvette beyond its saturation solubility, the absorbance baseline in the visible region shifted up due to scattering of light from the undissolved particles of the drug. None of the drugs or the dispersion carriers was found to absorb in the visible region. These solubility determinations were performed in triplicate using Gelucire 50/13 and PEG 1450 as the dispersion carriers at 60°C. PEG 1450 was used instead of the PEG 8000 (used in preparing the solid dispersion granules) due to problems encountered during stirring resulting from the high viscosity of the PEG 8000 melt. It has been reported that the dielectric constant of the PEGs does not depend on their average molecular weight but is rather a function of the concentration of its subunit (CH_2CH_2O) (21). The solubility of the drugs, therefore, should not be significantly different in PEG 1450 than in PEG 8000.

RESULTS

Ternary solid-dispersion granules of all the seven drugs were prepared by hot melt granulation using Gelucire 50/13 as the dispersion carrier and Neusilin US2 as the adsorbent. Dispersion granules of BAY 12-9566, naproxen, and progesterone were also prepared using PEG 8000 in place of Gelucire 50/13 as the dispersion carrier. Dissolution of BAY 12-9566 was further enhanced from the granules upon storage at 40°C/ 75% RH for 2 and 4 weeks (see Bay/G/N in Table I). Similar dissolution enhancement was also observed with

Table I. Drug Dissolution from Ternary Solid-Dispersion Granules: Comparison of Initial Dissolution Values with Those after Storage

	Percentage drug dissolved after 30 minutes (standard deviation)		
Batch name	Initial	2 Wk/40°C/ 75%RH	4 Wk/40°C/ 75%RH
Bay/G/N	39.5 (1.7)	82.0* (2.2)	82.7* (1.1)
Bay/P/N	39.7 (1.3)	64.3* (2.4)	69.8* (0.8)
Nap/G/N	37.6 (1.6)	54.4* (1.5)	54.7* (1.3)
Nap/P/N	44.2 (1.4)	41.0 (3.0)	43.0 (2.9)
Ket/G/N	92.7 (1.2)	91.3 (0.6)	91.8 (1.0)
Ind/G/N	67.9 (1.9)	66.3 (1.6)	63.5* (1.7)
Phe/G/N	97.0 (1.5)	85.6* (1.3)	86.2* (0.9)
Tes/G/N	56.0 (3.5)	51.0* (2.7)	43.2* (2.9)
Pro/G/N	73.0 (1.2)	46.7* (0.6)	39.4* (1.7)
Pro/P/N	45.3 (1.4)	45.5 (0.6)	42.9* (0.8)

Student's independent *t*-test was performed at an α-value of 0.05
* indicates significant difference between the initial and the stored granules.

naproxen (see Nap/G/N in Table I). Although ketoprofen granules (Ket/G/N) did not show any change in dissolution, indomethacin granules (Ind/G/N) showed a slight decrease in drug dissolution (see Ket/G/N and Ind/G/N in Table I). On the other hand, granules containing phenacetin, testosterone, and progesterone exhibited the more commonly reported decrease in the enhanced dissolution on storage (see Phe/G/N, Tes/G/N, and Pro/G/N, in Table I). The percentage drug dissolution (after 30 min) upon storage compared to the initial sample was calculated and is shown in Fig. 2. As shown in Fig. 2, the magnitude of changes in drug dissolution from PEG-containing dispersion granules was significantly less than that observed with Gelucire-containing granules. In the following sections, drug dissolution data is discussed relative to corresponding changes in hydrogen bonding (FT-IR studies), crystallinity of drug (XPD studies), melting point of the eutectic (MDSC studies), and the solubility data.

BAY 12-9566 Solid-Dispersion Granules

As shown in Table I, dissolution of BAY 12-9566 was enhanced further from the ternary solid-dispersion granules (Bay/G/N and Bay/P/N) after storage at 40°C/ 75% RH. Upon storage at 40°C/ 75% RH for 4 weeks, dissolution after 30 min was found to be 210% of the initial dissolution from granules, Bay/G/N (Fig. 2).

The hydrogen bonding interaction between BAY 12-9566 and Neusilin was explained in detail in a previous publication (6). BAY 12-9566, like many other carboxylic acid-containing drugs, exists as a dimer stabilized via intermolecular hydrogen bonding. In the crystalline state the characteristic dimer peak of the carboxylic acid group is at 1695 cm^{-1}, whereas in the amorphous state it is at 1707 cm^{-1} (6). As shown in Fig. 3, the dimer peak at 1695 cm^{-1} was only apparent as a shoulder in the spectrum for the initial granules (Bay/G/N), indicating a disruption of dimer hydrogen bonds. Further, upon storage at 40°C/ 75% RH for 4 weeks, the dimer peak disappeared and only one peak was observed at 1687 cm^{-1} (Fig. 3), indicating complete absence of any dimers. In the crystalline state, intramolecular hydrogen bonding is probable between oxygen of the benzoyl carbonyl and hydrogen of the carboxyl group of BAY 12-9566, leading to a peak at 1681 cm^{-1}. The blue shift for the benzoyl carbonyl stretching peak from 1681 cm^{-1} to 1687 cm^{-1} on storage is an indication of a tendency toward hydrogen bonding between BAY 12-9566 and Neusilin compared to that for intramolecular hydrogen bonding. Similar changes in FT-IR spectra for Bay/P/N granules indicate the presence of a further increase in the drug hydrogen-bonded to Neusilin upon storage in the presence of PEG as well (6).

XPD studies were performed to detect any changes in the crystallinity of BAY 12-9566, corresponding to the increased hydrogen bonding to Neusilin, indicated by FT-IR studies. The absence of any peaks in the diffractogram of Neusilin confirmed its amorphous nature (data not shown). The intensity of the most intense peak for crystalline BAY 12-9566, at a 2θ value of 20.8, was found to be dramatically reduced for the initial granules, Bay/G/N and Bay/P/N, indicating significant conversion to the amorphous state on formulation of solid-dispersion granules. Upon storage of these granules at 40°C/ 75% RH for 4 weeks, the intensity of this peak was found to decrease further (shown for granules, Bay/G/N, in Fig. 4). The increase in the amount of drug hydrogen-bonded to Neusilin is therefore accompanied by a corresponding decrease in the amount of crystalline BAY 12-9566 upon storage of granules.

However, the change in drug dissolution upon storage is greater for Gelucire-containing granules (Bay/G/N) than PEG-containing (Bay/P/N) granules. BAY 12-9566 showed good solubility in both Gelucire as well as PEG (Table II and Fig. 5). The onset of the melting point of the eutectic mixture of BAY 12-9566 and Gelucire 50/13 (30.2°C) was lower than that of the drug and PEG 8000 (37°C) (see Table II).

Naproxen Solid-Dispersion Granules

Like BAY 12-9566, naproxen is a carboxylic acid containing drug with the potential to accept as well as donate protons and hydrogen bond with Neusilin. Dissolution enhancement of naproxen was observed upon formulation as

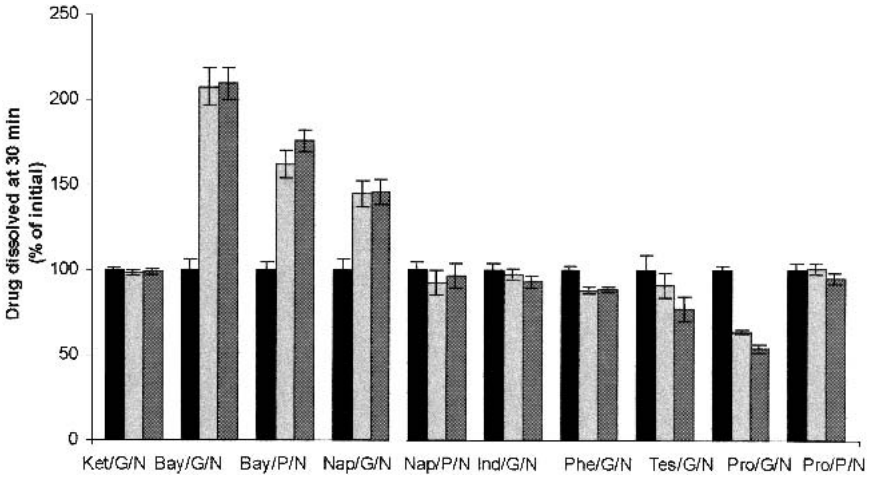

Fig. 2. Comparison of drug dissolution (after 30 min) from initial and stored solid-dispersion granules using USP Type II apparatus at 50 rpm. Data are shown for drug dissolution (% of initial) from solid-dispersion granules after storage at 40°C/ 75% RH: Initial (black); 2 weeks (gray); and 4 weeks (squares).

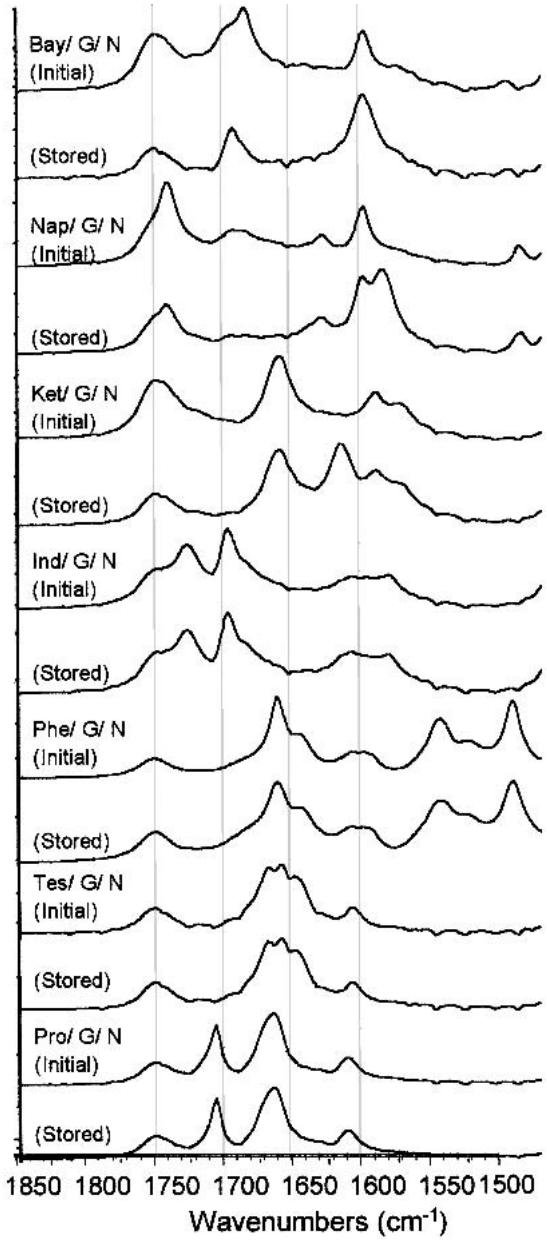

Fig. 3. FT-IR spectra for solid-dispersion granules before and after storage. Spectra are shown for granules: Bay/G/N, Nap/G/N, Ket/G/N, Ind/G/N, Phe/G/N, Tes/G/N, Pro/G/N.

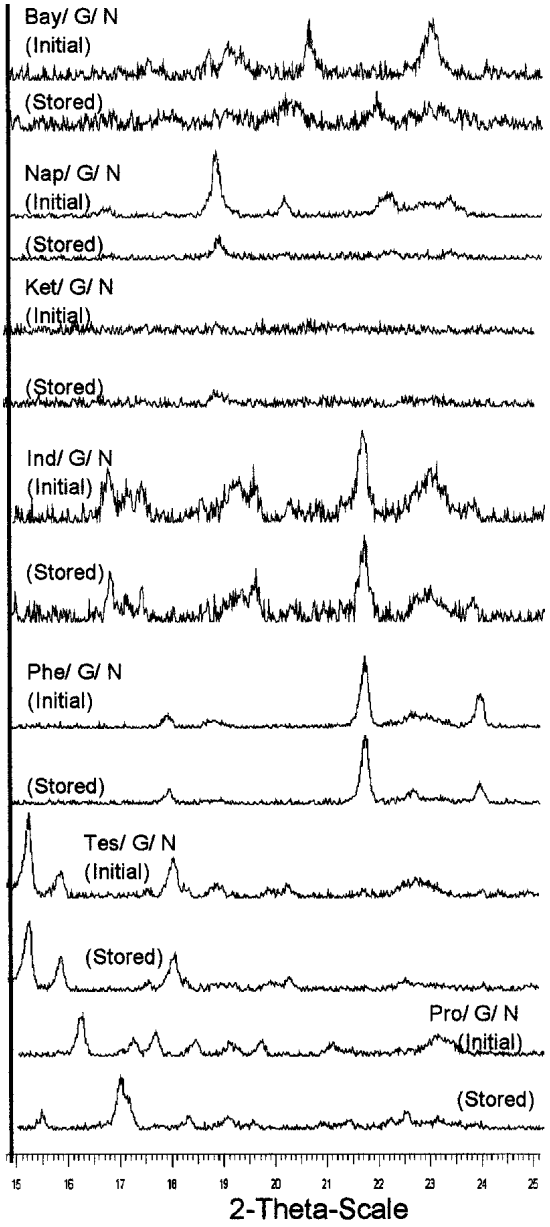

Fig. 4. X-ray diffractograms for solid-dispersion granules before and after storage. Spectra are shown for granules: Bay/G/N, Nap/G/N, Ket/G/N, Ind/G/N, Phe/G/N, Tes/G/N, Pro/G/N.

granules, Nap/G/N and Nap/P/N. In contrast to the further increase in dissolution from Gelucire-containing granules (Nap/G/N), the PEG-containing granules (Nap/P/N) did not show any change in drug dissolution on storage at 40°C/ 75% RH for 4 weeks (see Nap/G/N and Nap/P/N in Table I and Fig. 2).

As previously reported, FT-IR studies revealed the presence of hydrogen bonding between naproxen and Neusilin in the granules, Nap/G/N and Nap/P/N (6). As observed with BAY 12-9566, naproxen granules, Nap/G/N, showed a reduction in the dimer peak (at 1680 cm^{-1} in both crystal and amorphous state) upon formulation and a further reduction during storage (Fig. 3). Also the peak at 1605 cm^{-1} split and showed a new red shifted peak at 1593 cm^{-1} for the stored granules, indicating changes in the hydrogen bonding of drug upon storage. Naproxen in the granules was, therefore, found to hydrogen bond with Neusilin and the interaction increased during storage.

In the X-ray diffractogram, the intensity of the most intense peak of naproxen, at a 2θ value of 19.0 in the crystalline state, decreased significantly for the granules, Nap/G/N and Nap/P/N, indicating decreased crystallinity of naproxen upon formulation of granules. Drug crystallinity was found to decrease further upon storage of granules, Nap/G/N and Nap/P/N at 40°C/ 75% RH for 4 weeks (shown for granules, Nap/G/N, in Fig. 4). Similar to BAY 12-9566, a decrease in drug crystallinity accompanied by an increase in the hydrogen-bonded drug leads to the further enhancement in drug dissolution from naproxen granules upon storage.

The solubility of naproxen in Gelucire (14.0% w/w) is

Table II. Changes in State of Drug and in Drug Dissolution upon Storage of Ternary Solid-Dispersion Granules: Comparison of Initial Dissolution Values with Those after Storage

	Changes upon storage of dispersion granules				
Dispersion granules	Change in drug dissolution	Crystalline drug (XPD)	Drug hydrogen-bonded to Neusilin (FT-IR)	Onset of melting point of the eutectic (°C) (MDSC)	Solubility of the drug in the dispersion carrier (% w/w)
Bay/G/N	Increase	Decreases	Increases	30.2	33.8
Bay/P/N	Increase	Decreases	Increases	37.0	42.0
Nap/G/N	Increase	Decreases	Increases	30.5	14.0
Nap/P/N	No change	Decreases	Increases	38.0	20.6
Ket/G/N	No change	No change	No change	16.8	39.3
Ind/G/N	Decrease	No change	No change	30.4	10.0
Phe/G/N	Decrease	No change	No change	34.2	6.2
Tes/G/N	Decrease	No change	No change	35.5	3.0
Pro/G/N	Decrease	Complete β to α	No change	33.4	7.4
Pro/P/N	Decrease	Incomplete β to α	No change	39.0	8.3

less than that of BAY 12-9566 and ketoprofen, but is higher than the other four drugs used in this study (Fig. 5). Although the onset of melting of the eutectic mixture was 30.5°C in Nap/G/N, it was 38°C in the granules, Nap/P/N.

Ketoprofen Solid-Dispersion Granules

Dissolution of ketoprofen (a drug with a carboxylic acid group) was enhanced upon formulation as granules, Ket/G/N (data not shown). There was no change in drug dissolution from granules, Ket/G/N, upon storage for 4 weeks (see Table I and Fig. 2). Ketoprofen had the highest solubility in Gelucire (39.3% w/w) and showed the lowest onset of melting of the eutectic (16.8°C).

The FT-IR spectra showed the acid dimer peak at 1697 and 1706 cm^{-1} in the crystalline and the amorphous state of ketoprofen, respectively. Upon formulation as granules, Ket/G/N, the acid dimer peak disappeared, indicating breaking of the intermolecular hydrogen bonds and preferential hydrogen bonding between ketoprofen and Neusilin. As shown in Fig. 3, no further change in the dimer peak was observed upon storage of granules, Ket/G/N. In contrast to BAY 12-956 and naproxen, the amount of the ketoprofen hydrogen-bonded to Neusilin remains the same after storage for 4 weeks.

Upon formulation as granules, Ket/G/N, the X-ray diffractogram showed no peaks at all, indicating complete conversion to the amorphous state of the drug during initial processing of the granules (Fig. 4). No peaks were observed upon storage either (Fig. 4), indicating the absence of any reversion from the amorphous hydrogen bonded (to Neusilin) state to the crystalline state.

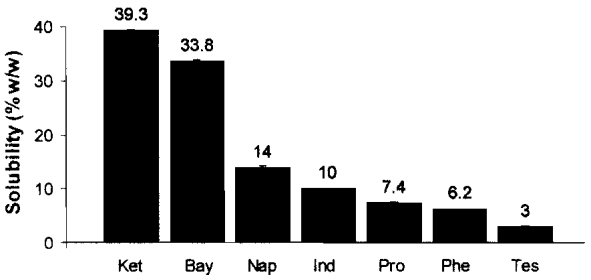

Fig. 5. Solubility (%w/w) of the seven drugs in Gelucire 50/13 at 60°C.

Indomethacin Solid-Dispersion Granules

Indomethacin is another drug with a carboxylic acid group. Similar to BAY 12-9566, naproxen, and ketoprofen, this drug also showed enhanced dissolution upon formulation as granules, Ind/G/N (data not shown). In contrast to the other three carboxylic acid containing drugs, a slight decrease in drug dissolution was observed upon storage of granules, Ind/G/N, at 40°C/ 75% RH for 4 weeks (see Table I and Fig. 2).

In the FT-IR spectrum, indomethacin showed the acid dimer peak at 1717 cm^{-1} and 1710 cm^{-1} for the crystalline and the amorphous state, respectively. Unlike BAY 12-9566, naproxen, and ketoprofen, which showed a red shift (from amorphous to crystalline state) in the acid dimer peak, indicating greater hydrogen bonding in the crystalline state, indomethacin does not seem to favor hydrogen bonding upon crystallization. Also, there was no reduction in the acid dimer peak at 1717 cm^{-1} for indomethacin granules, Ind/G/N, before or after storage (Fig. 3), indicating the absence of any changes in the hydrogen-bonded state of indomethacin.

From the XPD studies, it was found that drug was present at least in part in the crystalline state upon formulation as granules, Ind/G/N and the crystallinity did not change upon storage at 40°C/ 75% RH for 4 weeks (Fig. 4). The absence of any increase in drug crystallinity upon storage indicates the absence of any reversion from the amorphous to crystalline state. The onset temperature of the eutectic mixture was found to be 10°C lower than the storage temperature (see Table II). The solubility of indomethacin in Gelucire (10.0% w/w) was lower than the solubility of the other three carboxylic acid-containing drugs (Fig. 5).

Phenacetin Solid-Dispersion Granules

Phenacetin contains an amide group with a pKa of 2.2. Because the carboxylic acid-containing drugs were in the unionized state in 0.1 N HCl, it was decided to perform the dissolution studies for phenacetin in 0.05M phosphate buffer (pH 7) to keep the drug in an unionized state. Upon formulation as granules, Phe/G/N, drug dissolution was enhanced when compared to the drug alone (data not shown). However, dissolution was found to decrease significantly upon storage at 40°C/ 75% RH for 4 weeks (see Table I and Fig. 2).

Both the FT-IR spectra (Fig. 3) as well as XPD diffractograms (Fig. 4) did not show any evidence of changes in hydrogen bonding and drug crystallinity, respectively, upon storage at 40°C/ 75% RH for 4 weeks. Although the onset of melting of the eutectic was higher, the solubility of phenacetin in Gelucire was lower than that of indomethacin (Table II and Fig. 5).

Testosterone Solid-Dispersion Granules

Testosterone is a steroid compound containing a hydroxyl group. Similar to phenacetin, after the initial dissolution enhancement upon formulation as granules, Tes/G/N, dissolution was found to decrease significantly upon storage at 40°C/ 75% RH for 4 weeks (Table I and Fig. 2).

Similar to phenacetin granules, both the FT-IR spectra (Fig. 3) as well as XPD diffractograms (Fig. 4) of testosterone granules, Tes/G/N, did not show any evidence of changes in hydrogen bonding and drug crystallinity, respectively, upon storage at 40°C/ 75% RH for 4 weeks. The onset of melting of the eutectic of testosterone was higher than that of the eutectic of phenacetin (see Table II). The solubility of testosterone in Gelucire (3.0% w/w) was lowest among the seven drugs studied.

Progesterone Solid-Dispersion Granules

Progesterone does not have a proton-donating group but its carbonyl group can act as a proton acceptor. Progesterone granules, Pro/G/N and Pro/P/N, showed a decrease in dissolution upon storage at 40°C/ 75% RH for 4 weeks (see Table I). The magnitude of the decrease in dissolution upon storage of granules, Pro/G/N, was greater (54% of initial) than that of phenacetin or testosterone granules (Fig. 2). However, the magnitude of the change in dissolution upon storage of PEG-containing granules (Pro/P/N) was much less (95% of initial) than Gelucire-containing granules (Pro/G/N) (Fig. 2).

No changes in the FT-IR spectra of the granules, Pro/G/N, before or after storage, were found indicating the absence of any changes in the hydrogen-bonded state of the drug in granules (Fig. 3). Progesterone exists as the more stable (high melting point) α-form and the less stable (low melting point) β-form (22). The characteristic diffraction peak for the α-form seems at 2θ value of 16.9, whereas that for the β-form is at 16.1 (as noted from the Joint Committee of Powder Diffraction Standards, JCPDS database). It was found that the drug converted from the α-form to the more soluble β-form on formulation as granules, Pro/G/N (Fig. 4) and Pro/P/N. However, on storage the peak at 16.9 reappeared, indicating a reversion to the less soluble α-form (Fig. 4). The solubility of progesterone is similar in both Gelucire (7.4% w/w) and PEG (8.3% w/w). The onset of melting of the eutectic mixture in granules Pro/P/N was only 1°C below the storage temperature whereas for Pro/G/N it was 6.4°C below the storage temperature (see Table II).

DISCUSSION

Neusilin US2 was used as an adsorbent onto which the melt of the drug and the dispersion carrier was coated. With the silanol groups on its surface, Neusilin exhibits the potential to hydrogen bond with drugs having proton accepting and/or donating groups. In this study the generalizability of the previously proposed mechanism (6) of improved physical stability of the amorphous state via hydrogen bonding of the drug to Neusilin was investigated using seven drugs and two dispersion carriers. The changes in drug dissolution upon storage of dispersion granules were determined and the following modified mechanism was proposed to explain the dissolution based on supporting evidence from FT-IR, XPD, MDSC, and solubility studies.

As shown in Fig. 6, upon formulation of the solid-dispersion granules, each drug initially exists as a mixture of the crystalline state, A, the molecularly dispersed state in the dispersion carrier, B, and hydrogen bonded to Neusilin, C. The crystalline state includes the eutectic mixture of the drug with the dispersion carrier as well as the crystals of the drug in excess of eutectic composition. If the storage temperature is above the melting point of the eutectic mixture the melt of

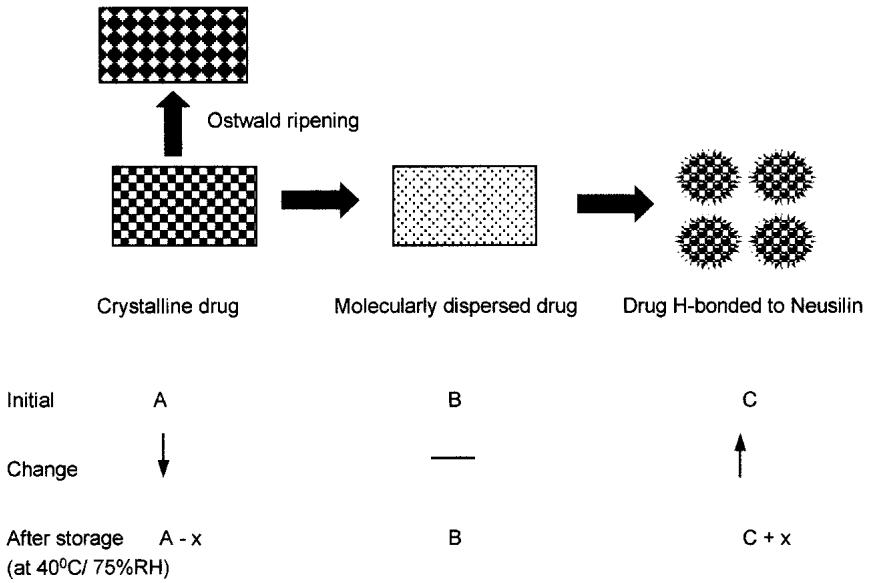

Fig. 6. Proposed mechanism for further increase in dissolution after storage.

the eutectic provides high mobility in the dispersion granules. The mobility in the melt (liquid) of a crystal is several orders of magnitude higher than that in a glass. The mobility in a supercooled liquid decreases several orders of magnitude upon glass formation and has been explained as a function of temperature relative to the glass transition temperature (23,24). In the present system, however, the increased mobility is a result of the melting point of the eutectic being lower than the storage temperature. At the storage temperature (40°C), the melt of the eutectic will add to the molecularly dispersed state (in the dispersion carrier) of drug, B. The melting point of the pure crystalline state of drugs is still far above the storage temperature.

When a drug is highly soluble (>10% w/w) in the dispersion carrier there is significant flux from the molecularly dispersed state of the drug, B, toward the surface of Neusilin to increase the amount of drug hydrogen bonded to Neusilin, C. Therefore, on storage, an amount, x, of drug hydrogen bonds with Neusilin, creating a concentration gradient in the molecularly dispersed state, thereby reducing the pure crystalline drug by an amount x. Consequently upon storage, there is an increase in the hydrogen bonded drug, C, and a decrease in the pure crystalline drug, A, the changes being mediated through the molecularly dispersed state, B. These changes manifest themselves as a further increase in drug dissolution upon storage of the granules.

When a drug has low solubility (<10% w/w) in the dispersion carrier there is no significant flux from the molecularly dispersed state of the drug, B, toward the surface of Neusilin. Therefore, there is no increase in the hydrogen-bonded state of the drug on storage. The drug that is already hydrogen bonded does not revert to the crystalline state either. In the absence of any reversion from the amorphous hydrogen-bonded Neusilin bound state, a competing mechanism operates to decrease drug dissolution on storage. Ostwald ripening leads to the growth of larger crystals at the expense of the smaller crystals and has been well documented in the literature (25–27). On storage, the microcrystals of the drug in the dispersion granules grow in size leading to decreased effective surface area of the drug, thereby decreasing drug dissolution. The diffusion pathlength for a molecularly dispersed drug molecule to reach another drug crystal within the dispersion coat is shorter compared to the pathlength to reach the surface of the adsorbent, Neusilin. Regardless of the solubility of drug in the dispersion carrier, Ostwald ripening will eventually occur. However, in cases where the drug has high solubility in the dispersion carrier any grown (ripened) drug crystals can redissolve and add to the molecularly dispersed state of the drug, ultimately diffusing to the surface of Neusilin, leading to the further enhancement in drug dissolution. Although a trend toward Ostwald ripening was observed from scanning electron microscopy (SEM) studies of the initial and the stored granules, no conclusive evidence could be documented due to the microporous and spherical nature of Neusilin. Thus, it seems that a competition between the driving force for hydrogen bonding with Neusilin and the phenomenon of Ostwald ripening ultimately determines the drug dissolution profile from the dispersion granules on storage. The solubility of the drug in the dispersion carrier is the key to which pathway predominates.

All the seven Gelucire-containing dispersion granules had a eutectic melting point below the storage temperature, 40°C. The liquid state of the eutectic greatly increases drug mobility in the dispersion granules to allow changes in the granules leading to changes in drug dissolution on storage. As shown in Fig. 5, solubility of drugs in Gelucire 50/13 followed the descending order: Ketoprofen > BAY 12-9566 > Naproxen > Indomethacin > Progesterone > Phenacetin > Testosterone. Bay/G/N and Nap/G/N dispersion granules showed an increase in dissolution upon storage at 40°C/ 75% RH up to 4 weeks. Because BAY 12-9566 showed a higher solubility in Gelucire than naproxen, the magnitude of increase in dissolution upon storage was greater for Bay/G/N granules (210% of initial) compared to Nap/G/N granules (145% of initial) (Fig. 2). A higher value of solubility in the dispersion carrier resulted in a greater magnitude of flux toward Neusilin, leading to the maximum enhancement in dissolution observed upon storage for Bay/G/N (Fig. 2). Although, ketoprofen had the highest solubility in Gelucire 50/13 (39.3% w/w) and Ket/G/N granules showed the lowest onset of melting of the eutectic (16.8°C), there was no change in drug dissolution from granules upon storage for 4 weeks (see Table I). The FT-IR and XPD data give evidence for a complementary explanation. Upon formulation as granules, Ket/G/N, the diffractogram showed no peaks at all, indicating complete conversion to the amorphous state of the drug during processing (Fig. 4). Further decrease in the crystalline state and a concomitant increase in the hydrogen-bonded (to Neusilin) state upon storage are not possible if the drug does not exist in the crystalline state even in the initial granules. The absence of crystalline state explains the absence of any further increase in drug dissolution upon storage of granules, Ket/G/N. On the other hand, hydrogen bonding of ketoprofen with Neusilin blocks any reversion to the crystalline state that could have led to a decrease in drug dissolution. In the absence of any crystals, Ostwald ripening is not possible either.

Although, indomethacin is similar to the other carboxylic acid-containing drugs in that it has the potential to hydrogen bond with Neusilin, hydrogen bonding does not seem to occur in the presence of Gelucire 50/13. The solubility of indomethacin in Gelucire 50/13 was the least (10.0% w/w) when compared to the other carboxylic acid-containing drugs (Fig. 5). Indomethacin therefore does not exist in the molecular state in a high enough concentration to allow significant flux toward the surface of Neusilin. Although there is sufficient mobility in the molten eutectic during storage, it is the limited solubility of indomethacin in Gelucire 50/13 that allows a competitive balance between the two phenomena of hydrogen bonding with Neusilin and Ostwald ripening, leading to only a slight decrease in dissolution upon storage (probably due to Ostwald ripening).

On the other hand, phenacetin, testosterone, and progesterone showed significant decreases in drug dissolution upon storage of Phe/G/N, Tes/G/N, and Pro/G/N, respectively (Fig. 2). During storage, the eutectic mixtures in these three granules were found to exist in the liquid state allowing sufficient mobility for diffusion of the molecularly dispersed state of drug (see Table II). However, the solubility of these drugs in Gelucire was poor: phenacetin (6.2% w/w), testosterone (3.0% w/w), and progesterone (7.4% w/w). The poor solubility of these drugs in Gelucire did not allow sufficient flux toward the surface of Neusilin. This limitation allowed Ostwald ripening to be the dominant mechanism leading to de-

creased surface area of the microcrystalline drug resulting in decreased drug dissolution upon storage. In the same rank order with the solubility values, the magnitude of the decrease in drug dissolution upon storage for 4 weeks was greater for testosterone granules (77% of initial) when compared to the phenacetin granules (89% of initial). Although the solubility of progesterone in Gelucire was higher than that of phenacetin and testosterone, the granules, Pro/G/N showed the greatest decrease in drug dissolution (54% of initial).

Other factors responsible for the additional decrease in drug dissolution from progesterone granules, Pro/G/N were investigated. On storage progesterone reverted to the less soluble α-form, thereby, decreasing drug dissolution on storage (Fig. 4). Conversion from the more soluble to the less soluble polymorph (β to α) explains the additional decrease in drug dissolution upon storage of granules, Pro/G/N, when compared to phenacetin and testosterone granules. It was therefore found that the rank order for the change in dissolution upon storage (Fig. 2) follows that of the solubility of the drugs in Gelucire (Fig. 5). Progesterone showed additional decrease in dissolution due to the polymorphic conversion. These results are summarized in Table II.

Dispersion granules for BAY 12-9566, naproxen, and progesterone were also prepared using PEG 8000 in place of Gelucire 50/13. The magnitudes of changes in dissolution were greater for Gelucire-containing granules (Bay/G/N, Nap/G/N, and Pro/G/N) than PEG-containing granules (Bay/P/N, Nap/P/N, and Pro/P/N) (Fig. 2). The solubility of these three drugs was higher in PEG than in Gelucire (see Table II), thereby, allowing the possibility of flux from the molecularly dispersed state toward the surface of Neusilin during storage of granules. However, the eutectic mixtures in the PEG containing granules showed the onset of melting at temperatures very close to that of the storage temperature. It was found that the onset of the melting point of the eutectic mixture of BAY 12-9566 and Gelucire (30.2°C) was lower than that with PEG (37°C). Similar trends were observed for naproxen and progesterone granules as well (see Table II). The onsets of melting point for these eutectics are all below the storage temperature, 40°C. The eutectic mixture, therefore, exists in the liquid state in these granules. It should, however, be noted that at a particular temperature, the viscosity of PEG 8000 is much greater compared to Gelucire 50/13 (comprises esters of PEG 1500). In fact at a temperature of 70°C, Gelucire showed a viscosity of 49 cps (28), compared to approximately 2000 cps for PEG 8000 (29), a difference of 40 fold. Additionally, the difference in the onset of melting point of the eutectic mixtures leads to a higher viscosity and a lower mobility in the PEG 8000 containing granules. This phenomenon seems responsible for the kinetic limitation imposed upon PEG containing granules during storage. The lower mobility in PEG containing granules, Bay/P/N, Nap/P/N, and Pro/P/N seems to limit the change in dissolution compared to Gelucire containing granules, Bay/P/N, Nap/P/N, and Pro/P/N, over the same 4 week storage period (Fig. 2).

CONCLUSIONS

Upon storage at 40°C/ 75% RH up to 4 weeks, ternary dispersion granules of drug/ Gelucire 50/13/ Neusilin exhibit no change in drug dissolution for ketoprofen, an increase for BAY 12-9566 and naproxen, a slight decrease for indomethacin and significant decrease for phenacetin, testosterone, and progesterone. Two competing mechanisms have been proposed to explain the changes in drug dissolution upon storage of solid dispersion granules. Conversion of the crystalline drug to the amorphous hydrogen bonded (to Neusilin) state seems to increase dissolution, whereas, the phenomenon of Ostwald ripening can be used to explain the decrease in drug dissolution upon storage. The solubility of the drug in Gelucire 50/13 is a crucial factor in determining the predominant mechanism by governing the flux toward the surface of Neusilin. A kinetic limitation seems responsible for a lesser magnitude of change in drug dissolution from the PEG-containing granules when compared to the Gelucire-containing granules.

In this study we have investigated the underlying mechanisms resulting in changes in drug dissolution on storage. It should be noted that changes in drug dissolution on storage are not desirable. A physically stable system, such as that for ketoprofen (Ket/G/N) in the present study, may be achieved by increasing time of granulation, annealing, increasing temperature during granulation, etc. These approaches can potentially result in a formulation with increased as well as stable drug dissolution.

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REFERENCES

1. J. L. Ford. The current status of solid dispersions. *Pharm. Acta Helv.* **61**:69–88 (1986).
2. W. L. Chiou and S. Riegalman. Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* **60**:1281–1302 (1971).
3. A. T. M. Serajuddin. Solid dispersions of poorly water-soluble drugs: Early promises, Subsequent problems, and recent breakthroughs. *J. Pharm. Sci.* **88**:1058–1066 (1999).
4. C. Leuner and J. Dressman. Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Bio.* **50**:47–60 (2000).
5. M. K. Gupta, D. Goldman, R. H. Bogner, and Y. Tseng. Enhanced drug dissolution and bulk properties of solid dispersions granulated with a surface adsorbent. *Pharm. Dev. Technol.* **6**:563–572 (2001).
6. M. K. Gupta, R. H. Bogner, D. Goldman, and Y. Tseng. Mechanism for further enhancement in drug dissolution from solid-dispersion granules. *Pharm. Dev. Technol.* **7**:103–112 (2002).
7. I. Chang and G. E. Maciel. Probing hydrogen bonding and the local environment of silanols on silica surfaces via nuclear spin cross polarization dynamics. *J. Am. Chem. Soc.* **118**:401–406 (1996).
8. I. Chang and G. E. Maciel. A detailed model of local structure and silanol hydrogen bonding of silica gel surfaces. *J. Phys. Chem. B.* **101**:3052–3064 (1997).
9. T. Watanabe, N. Wakiyama, F. Usui, M. Ikeda, T. Isobe, and M. Senna. Stability of amorphous indomethacin compounded with silica. *Int. J. Pharm.* **226**:81–91 (2001).
10. T. Matsumoto and G. Zografi. Physical properties of solid molecular dispersions of indomethacin with poly(vinylpyrrolidone) and poly(vinylpyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization. *Pharm. Res.* **16**:1722–1728 (1999).
11. F. Pozzi, A. Longo, C. Lazzarini, and A. Carenzi. Formulations of ubidecarenone with improved bioavailability. *Eur. J. Pharm. Biopharm.* **37**:243–246 (1991).
12. P. C. Sheen, S. I. Kim, J. J. Petillo, and A. T. M. Serajuddin.

Bioavailability of a poorly water-soluble drug from tablet and solid dispersion in humans. *J. Pharm. Sci.* **80**:712–714 (1991).
13. D. Q. M. Craig. Polyethylene glycols and drug release. *Drug Dev. Ind. Pharm.* **16**:2501–2526 (1990).
14. J. C. Price. Polyethylene glycol. In: A. Wade and P. J. Weller (eds.), *Handbook of Pharmaceutical excipients*, The Pharmaceutical Press, London, 1994 pp. 355–361.
15. Company literature on Neusilin. Fuji Chemical Industry Co. Ltd., Toyama Japan, pp. 3–4.
16. L. S. Taylor and G. Zografi. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.* **14**:1691–1698 (1997).
17. N. Hirasawa, K. Danjo, M. Haruna, and A. Otsuka. Physicochemical characterization and drug release studies of naproxen solid dispersions using lactose as a carrier. *Chem. Pharm. Bull.* **46**:1027–1030 (1998).
18. R. M. Silverstein, G. C. Bassler, and T. C. Morrill. *Spectrometric identification of organic compounds*, John Wiley and Sons, Inc., New York, 1991.
19. R. Suryanarayanan. X-ray powder diffractometry. *Drugs Pharm. Sci* **70**:187–221 (1995).
20. R. Duclos, J. Grenet, J. M. Saiter, P. Besancon, and A. M. Orecchioni. Effect of ageing on progesterone-polyethylene glycol 6000 dispersions, X-ray study. *Drug Dev. Ind. Phar* **16**:255–265 (1990).
21. K. Arnold, A. Herrman, L. Pratsch, and K. Gawrisch. The dielectric properties of aqueous solutions of poly (ethylene glycol) and their influence on membrane structure. *Biochim. Biophys. Acta* **815**:515–518 (1985).
22. M. Muramatsu, M. Iwahashi, and U. Takeuchi. Thermodynamic relationship between α and β-forms of crystalline progesterone. *J. Pharm. Sci.* **68**:175–177 (1979).
23. S. Shamblin, X. Tang, L. Chang, B. Hancock, and M. J. Pikal. Characterization of the time scales of molecular motion in pharmaceutically important glasses. *J. Phys. Chem. B* **103**:4113–4121 (1999).
24. P. Tong and G. Zografi. Solid state characteristics of amorphous sodium indomethacin relative to its free acid. *Pharm. Res.* **16**: 1186–1192 (1999).
25. J. A. Searles, J. F. Carpenter, and T. W. Randolph. Annealing to optimize the primary drying rate, reduce freezing induced drying rate heterogeneity, and determine Tg' in pharmaceutical lyophilization. *J. Pharm. Sci.* **90**:872–887 (2001).
26. W. Bender and L. Ratke. Ostwald ripening of liquid phase sintered Cu-Co dispersions at high volume fractions. *Acta Matter* **46**:1125–1133 (1998).
27. A. J. Ardell. Microstructural stability at elevated temperatures. *J. Eur. Ceramic Soc.* **19**:2217–2231 (1999).
28. H. Eliasen, T. Schaefer, and H. G. Kristensen. Effects of binder rheology on melt agglomeration in a high shear mixer. *Int. J. Pharm.* **176**:73–83 (1998).
29. Company literature on Carbowax. *Polyethylene glycols and methoxypolyethylene glycols*, Union Carbide, Danbury, Connecticut, pp. 15–17.