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Evaluation of polar lipid–hydrophilic polymer microparticles

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Abstract

The aim of the present study was to prepare controlled-release tablets of poorly-soluble drug, felodipine. Spray chilling was used to formulate the drug, the polar lipids and the hydrophilic polymers into solid dispersion microparticles, which were then compressed. The microparticles were characterised by Fourier transform infrared and Raman spectroscopies, X-ray powder diffraction, hot-stage microscopy, scanning electron microscopy, and image analysis. The crystallinity of felodipine had decreased in all the samples, and the amount of crystalline felodipine varied depending on the composition of the solid dispersion. The particles were spherical with the median particle diameter ranging from 20 to 35 μm. The addition of hydrophilic polymer into the matrix widened the particle size distribution and increased the amount of agglomerates. Most promising dissolution patterns were obtained from tablets containing glycerides; e.g. from Precirol® ATO 5/Pluronic® F127 tablets the release was of zero order.

Keywords: Controlled release; Felodipine; Hydrophilic polymer; Polar lipid; Solid dispersion; Spray chilling

1. Introduction

Solid dispersions have been reviewed by Chiou and Riegelman (1971) and Ford (1986). Solid dispersions are usually prepared using a melt or a solvent method. The advantage in melt method is that no organic solvents are needed. On the other hand, the drug substance cannot be temperature sensitive. The conventional melt method is a multi-stage process, because, after solidification, the product has to be pulverised before compressing it to produce tablets or filling it into capsules. Therefore, many improvements to the melt method have been presented in the literature, e.g. melt extrusion (Prapaitrakul et al., 1991; Follonier et al., 1994), filling of hard gelatin capsules with the melt (Bodmeier et al., 1990) and spray chilling (Killeen, 1993).

Solid dispersion techniques offer an interesting formulation approach not only for enhancing drug solubility but also for controlling the release rate of the drug. The advantage in solid dispersion controlled-release formulations is that a matrix type system is formed. Thus, the risk of dose dumping is avoided. Both polymers (Ozeki et al., 1999; Ozeki et al., 2000) and lipids have been used as matrix forming materials. Blends of waxes with different HLB

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values (Bodmeier et al., 1990; Bruguera et al., 1990; Dennis et al., 1990) or melting points (Sakamoto et al., 1991) have been combined in various ratios to obtain a desired release profile. Parab et al. (1986) used the melt method to prepare solid dispersion granules of Precirol® ATO 5 and theophylline. The release rate was adjusted by adding hydrophilic excipient mannitol or hydroxypropyl methylcellulose 4000 (HPMC) to the solid dispersion granules by mechanical activation. Malamataris et al. (1991) modified the release pattern by mixing different dissolving or swelling direct compression excipients with solid dispersion granules made of palmitostearate and dipophylline granules before compressing the mass into tablets. Spray chilling has been used previously to prepare controlled-release particles of polar lipids (Cusimano and Becker, 1968; Akiyama et al., 1993; Rodriguez et al., 1999). Cusimano and Becker (1968) added a surfactant sorbitan monostearate and Akiyama et al. (1993) added lactose to the molten lipid to adjust the release rate.

Hydrophilic polymers, like polyethylene glycols (PEG) or polyvinylpyrrolidone (PVP) are among the popular carriers commonly used to prepare solid dispersions. Being freely soluble in water, both of the polymers have mainly been used as excipients, both alone and in combination with other excipients, to enhance the dissolution rate of drugs (Ginés et al., 1995; Perng et al., 1998; Martínez-Ohárriz et al., 1999; Nair et al., 2002). Also surfactants, such as Poloxamers, which are a polyoxyethylene (PEO)–polyoxypropylene (PPO) copolymers, have been used for the same purpose (Kerč et al., 1993). Pluronic® F68 (Poloxamer 188) and Gelucire® 50/13, which is a mixture of mono- di- and tri-glycerides and PEG esters of fatty acids (HLB value 13), were used to form a solid dispersion to enhance the dissolution rate of poorly water soluble nifedipine (Vippagunta et al., 2002). However, hydrophilic polymers have not been combined before with lipids at molten state to form controlled-release microparticles. Thus, this principle has been filed as a patent application (Juppo, 2002).

The term solid dispersion covers a wide range of systems, where both the drug and the excipients can be in either crystalline or amorphous state or molecularly dispersed in a matrix (Chiou and Riegelman, 1971; Ford, 1986). Different possibilities to stabilise the system have been presented in literature (Frömming and Hosemann, 1985; Yu, 2001). Excipients are often added to amorphous drugs to increase the stability. Stability is increased due to a decrease in molecular mobility. Also direct drug-excipient interactions, like hydrogen bonding, are important. The molecular interactions are the basis for the formation of solid dispersions, and a requirement for the formation of a stable state.

In our previous study we used the spray chilling method to prepare controlled-release tablets of felodipine and polar lipids (Savolainen et al., 2002). In the present study our aim was to study whether the release rate could be further adjusted by adding a hydrophilic polymer into the solid dispersion matrix of the lipid and felodipine and to characterise the solid state of the drug.

2. Materials and methods

2.1. Materials

Felodipine was obtained from AstraZeneca (Sweden). Lipophilic excipients chosen for this study represented different groups of polar lipids: fatty alcohols, fatty acids, fatty acid esters, hydrogenated fatty acid esters and polar waxes (Table 1). Lipophilic excipients cetanol (Nacol 16–95) and glyceryl monostearate were purchased from Condea Chemie GmbH (Germany), stearic acid from Scharlau Chemie S.A. (Spain), and carnauba wax from Frank B. Ross (USA). Compritol® 888 ATO, Precirol® ATO 5 and Precirol® WL 2155 ATO were obtained as a kind gift from Gattefosse (France). Hydrophilic polymers used were polyethylene glycol 4000 (PEG 4000, Clariant AB, Sweden) and Poloxamer 407 (Pluronic® F127, BASF AG, Germany), which is a polyoxyethylene (PEO)–polyoxypropylene (PPO) copolymer. Microcrystalline cellulose (Avicel® PH101, FMC International, Ireland) was used as a tablet diluent and sodium stearyl fumarate (MOEHS, Spain) as a lubricant.

2.2. Preparation of microparticles

In spray chilling technique, lipophilic material was melted at 110 °C and felodipine was dissolved into it. For carnauba wax temperature of 120 °C was needed to dissolve felodipine. After felodipine had

Table 1
Classification of the lipophilic excipients used in this study

Category	Lipid	Description
Fatty alcohol	Cetanol	Cetyl alcohol, C16 alcohol
Fatty acid	Stearic acid	C18 acid
Fatty acid esters of glycerol	Compritol® 888 ATO	Glyceryl behenate
	Glyceryl monostearate	
	Precirol® ATO 5	Glyceryl palmitostearate
	Precirol® WL 2155 ATO	Glyceryl ditristearate
Polar wax	Carnauba wax	A complex mixture containing, e.g. esters of acids and hydroxyacids

dissolved hydrophilic excipient was added. Compositions of the different microparticle samples are listed in Table 2. The melted mixture was kept at 110 °C (120 °C, when carnauba wax was used) and atomised with a specially constructed pneumatic nozzle (AstraZeneca R&D, Mölndal, Sweden) into a vessel in a carbon dioxide ice bath (temperature −50 °C). The inner diameter of the pneumatic nozzle was 1.0 mm, the capillary length was 5 mm, and the atomising gap was 2.4 mm. The atomisation air temperature was 400 °C and the pressure was 7 bar. The particles were collected and dried for approximately 18 h in a vacuum oven (Heraus Instruments and Labinett MD 4C vacuum pump, Vacuumbrand GmbH & Co., Germany) at 25 °C. Dried samples were stored in a desiccator.

2.3. Preparation of melts

For powder XRD and FT-Raman analysis lipophilic material was melted at 110 °C (120 °C, when carnauba wax was used). Drug substance was then added to the melt. After felodipine had dissolved, the hydrophilic excipient was added. The weight ratio of the drug to the lipophilic and to the hydrophilic excipient was 1:4:2 (w/w/w) (Table 2, experiments 1–6). When the hydrophilic excipient had melted completely, the melt was quickly poured on a teflon plate, which was kept in carbon dioxide ice. The temperature of the plate was −40 °C. The melt was allowed to cool for 10 min before breaking it into pieces. Placebo melts, containing only hydrophilic and lipophilic excipients in weight ratio 1:2 (w/w), were prepared in the same manner. For the FT-IR melts containing only felodipine and hydrophilic excipient were prepared (1:2, w/w). The samples were stored in a desiccator.

2.4. Preparation of physical mixtures

Physical mixtures of felodipine with PEG 4000 or Pluronic® F127 (1:2, w/w) were prepared to be used for comparison in the FT-IR analysis. PEG 4000 and Pluronic® F127 were first ground in a mortar and sieved through a 350 μm sieve. The sieved excipient

Table 2
Compositions of the microparticle/melt samples

Experiment	Drug	Lipophilic excipient	Hydrophilic excipient	Ratio
1	Felodipine	Carnauba wax	Pluronic® F127	1:4:2
2	Felodipine	Cetanol	PEG 4000	1:4:2
3	Felodipine	Cetanol	Pluronic® F127	1:4:2
4	Felodipine	Precirol® ATO 5	Pluronic® F127	1:4:2
5	Felodipine	Stearic acid	PEG 4000	1:4:2
6	Felodipine	Stearic acid	Pluronic® F127	1:4:2
7	Felodipine	Compritol® 888 ATO	Pluronic® F127	1:4:2
8	Felodipine	Glyceryl monostearate	Pluronic® F127	1:4:2
9	Felodipine	Precirol® WL 2155	Pluronic® F127	1:4:2
10	Felodipine	Precirol® WL 2155	Pluronic® F127	1:2.42:1.21
11	Felodipine	Stearic acid	Pluronic® F127	1:3:3

was then mixed with sieved felodipine. The samples were stored in a desiccator.

2.5. Preparation of tablets

The microparticle samples were compressed into tablets with a weight of 200 mg each, and had a theoretical felodipine content of 10 mg. The tablets compressed from the particles of experiment 11 (Table 2) had a theoretical felodipine content of 15 mg. The compressed tablets contained 35% microparticles and 65% microcrystalline cellulose (Avicel® PH101). Reference tablets containing 10 mg felodipine and 190 mg microcrystalline cellulose (Avicel® PH101) were made for dissolution studies.

The microparticles were blended with microcrystalline cellulose and sodium stearyl fumarate (0.14% of the total weight of the mixture) in a Turbula mixer (Turbula 72C, Willy A Bachofen AG, Switzerland) for 10 min. The tablet mass of each tablet was weighed separately and compressed with an eccentric tablet press (Kilian SP300, Kilian & Co GmbH, Germany (experiments 1–6); Korsch EK 0, Korsch Maschinefabrik, Germany (experiments 7–11)) into a tablet using 10.0 mm flat-faced punches. The targeted breaking force of the tablets was 90 ± 5 N (Schleuniger Tablet Hardness Tester 4 M, Dr. Schleuniger Productronic AG, Switzerland). Therefore, with Kilian SP300 tablet press, the upper and lower punch distance was varied from 1.05 to 2.25 mm to control the tablet hardness. The minimum punch distance was 1.05 mm. In the cetanol + Pluronic® F127 and Precirol® ATO 5 + Pluronic(r) F127 samples, the punch distance could not be adjusted so that the targeted breaking force could be obtained. In these samples, the breaking force remained at 43–78 N. Before further analysis, the samples were stored in a desiccator in room temperature.

2.6. Fourier transform Raman spectroscopy (FT-Raman)

FT-Raman spectra were obtained on a Perkin Elmer System 2000 NIR FT-Raman (Perkin Elmer Co., USA) to characterise the solid-state form of felodipine in the melted samples. The analysis was performed about 2 months after sample preparation. Each sample was scanned 128 times and the spectrum was recorded between 0 and 4000 cm^{-1}. The spectra of the melted felodipine samples were compared with the spectra of placebo samples and the spectra of both crystalline and amorphous felodipine.

2.7. X-ray powder diffraction (XRPD)

The crystal properties of melted felodipine and placebo samples were studied after about 2 months in storage using XRPD (Diffractometer D5000, Siemens GmbH, Germany). A copper targeted X-ray tube (wavelength 0.1541 nm) was operated at a power of 40 kV × 50 mA. The measurements were performed at 2θ range 1–50° with a step size of 0.02° and a measuring time of 4 s per step. For X-ray powder diffraction analysis, the melted sample was gently ground in a mortar to obtain a powder. The sample was then prepared by loosely pressing about 400 mg powder into a sample holder. The diffractograms of the melted felodipine samples were compared with the diffractograms of placebo melts and crystalline felodipine.

2.8. Hot-stage microscopy (HSM)

The spray chilled particle samples (experiments 1–6, Table 2) were examined in a hot-stage microscope (Olympus BX50 optical microscope, Olympus Optical Co., Japan combined with a Linkam THMS 600 heating unit, Linkam Scientific Instruments Ltd., UK). The analysis was performed over 2 months after particle preparation. The samples were heated at 20 °C/min until the excipients had melted (60–95 °C) and the temperature was then kept constant for a minute for photographing. The microscope was combined with a frame grabber. Pictures of the sample were taken after the excipients had melted to see whether any crystals of felodipine could be seen. Since the melting temperature of crystalline felodipine is 144 °C and the excipients melted at markedly lower temperature, crystalline felodipine could be seen in the microscope if felodipine and the excipient had not formed a solid solution. For comparison, HSM pictures of the particles containing only lipophilic excipients were drawn from a previous publication (Savolainen et al., 2002).

2.9. Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectroscopy was used to determine the existence of interactions between felodipine and hydrophilic excipients in the melted samples using the method described by Savolainen et al. (2002). The interactions between felodipine and lipophilic excipient were determined previously (Savolainen et al., 2002). Since tertiary systems are difficult to interpret, to simplify binary systems of the drug and the excipient were studied.

2.10. Scanning electron microscopy (SEM)

A scanning electron microscope (JEOL JSM-5400 scanning microscope, Japanese Electron Optics Laboratory Co. Ltd., Japan) was used to examine the spray-chilled particles after about 2 months' storage (experiments 1–6, Table 2). SEM was combined with a frame grabber (JEOL Semafore, Version 2.0, J. Rimppi Oy, Finland). The samples were sputtered with gold for 15 min (JEOL JFC-1100E ion sputtering device, Japanese Electron Optics Laboratory Co. Ltd., Tokyo, Japan) before characterisation with SEM. The current used for sputtering was 10 mA and the sputtering gas was argon. SEM micrographs for the particles containing only lipophilic excipients were obtained from Savolainen et al. (2002).

2.11. Image analysis

Information about the particle size distribution and the roundness of the particles was obtained using an image analysis system (BeadCheck^{TM} 830, Pharma Vision Systems AB, Sweden). From each of the experiments 1–6 (Table 2) a number of 5000 particles and from each of the experiments 7–11 a number of 10,000 particles were analysed. For comparison, image analysis data for the particles containing only lipophilic excipients was drawn from Savolainen et al. (2002).

2.12. Drug content and dissolution

The drug content and dissolution analyses were performed from tablets using a method described previously (Savolainen et al., 2002). The rate of drug release was tested using the USP II paddle method about 1.5 months after particle preparation. The dissolution test from each batch was performed in triplicate. Dissolution data of the tablets containing only lipophilic excipients was obtained for comparison from a previous publication (Savolainen et al., 2002).

3. Results and discussion

3.1. FT-Raman

FT-Raman spectra of the samples were obtained to provide information about the crystallinity of the samples. All the samples contained felodipine that was similar to amorphous in the region of 3500–3000 cm^{-1} (Fig. 1) and similar to crystalline in the region of 1800–1400 cm^{-1} (Fig. 2). Therefore, the crystalline felodipine observed was not the same as the original crystal modification of felodipine. Since the same phenomenon could be seen in all the samples, it was not possible to say which sample was most crystalline and which was most amorphous.

3.2. Powder XRD

Each powder XRPD diffractogram of the felodipine melts was compared with the respective diffractogram of placebo melt and the diffractogram of crystalline felodipine to get more information about the felodipine crystallinity. In all the samples, the answer was inconclusive. The original polymorph of felodipine could not be determined in the samples as some of the peaks caused by the original crystalline modification of the felodipine were not determined in the melted samples. However, it may be possible that felodipine was not completely amorphous in some of the samples, since there were peaks in the felodipine melts which did not show up in the placebo melts. The peaks may be caused by an unknown polymorph of felodipine, since some of the new peaks are overlapping in all the samples regardless of the excipients. Another possibility is that the addition of felodipine to the melt changes the polymorphic form of the matrix materials.

Powder XRD and FT-Raman did not provide a clear answer about the crystallinity of the samples. It appears that samples are partly amorphous but may also have some crystalline felodipine of an unknown polymorph.

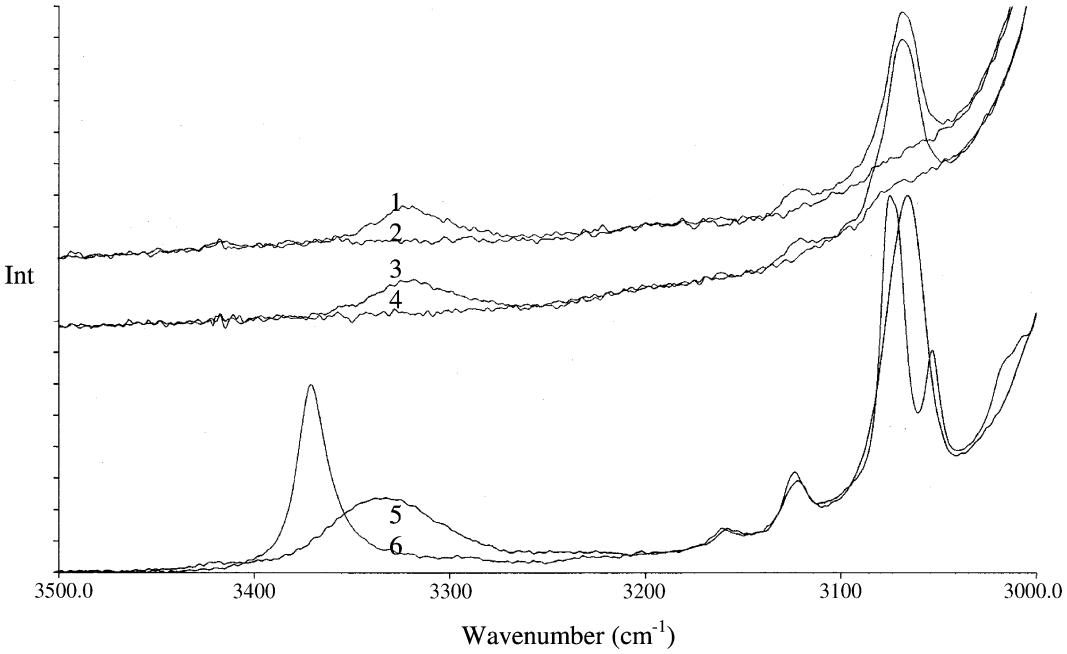

Fig. 1. FT-Raman spectra in the frequency of 3500–3000 cm^{-1}.

3.3. HSM

HSM is often combined with differential scanning calorimetry (DSC) to characterise the solid state form of the drug in solid dispersions (Ginés et al., 1995; Vélaz et al., 1998). The results of hot-stage microscopy results should be interpreted with care, as only a few particles from each sample were examined. Nevertheless, this examination can still provide some idea about the differences in crystallinity between the samples. Amorphous felodipine in a formulation is favoured as the dissolution rate of glassy felodipine is 3.8 times faster than that of crystalline felodipine (Kerč et al., 1991). An examination of the samples under the hot-stage microscope showed that the amount of crystalline felodipine varied from sample to sample. The amount of crystalline felodipine appeared to decrease, when the hydrophilic excipients were added to the melt, compared to the results obtained earlier from particles without the hydrophilic excipients (Savolainen et al., 2002). This trend was not as clear in the cetanol + PEG 4000 sample (Fig. 3), but in all other particles with hydrophilic excipients there was a notable decrease in the amount of crystalline felodipine (Fig. 4). Hardly any crystalline felodipine could be seen in the carnauba wax + Pluronic® F127 sample.

Based on the powder XRD and FT-Raman analysis, it seemed as a change in the felodipine polymorph might have occurred during the processing. This unknown polymorph could also have a higher solubility in the carrier materials than the original polymorph. Less crystalline felodipine is therefore seen in the particle samples in the HSM. As the matrix melts, felodipine might dissolve into it simultaneously.

3.4. FT-IR

In the felodipine molecule, the groups in which hydrogen bonding can occur are the amine group in the ring and the two carbonyl groups. When hydrogen bonding occurs, bond energy at the N–H or C=O bond decreases and a peak shift to lower frequencies

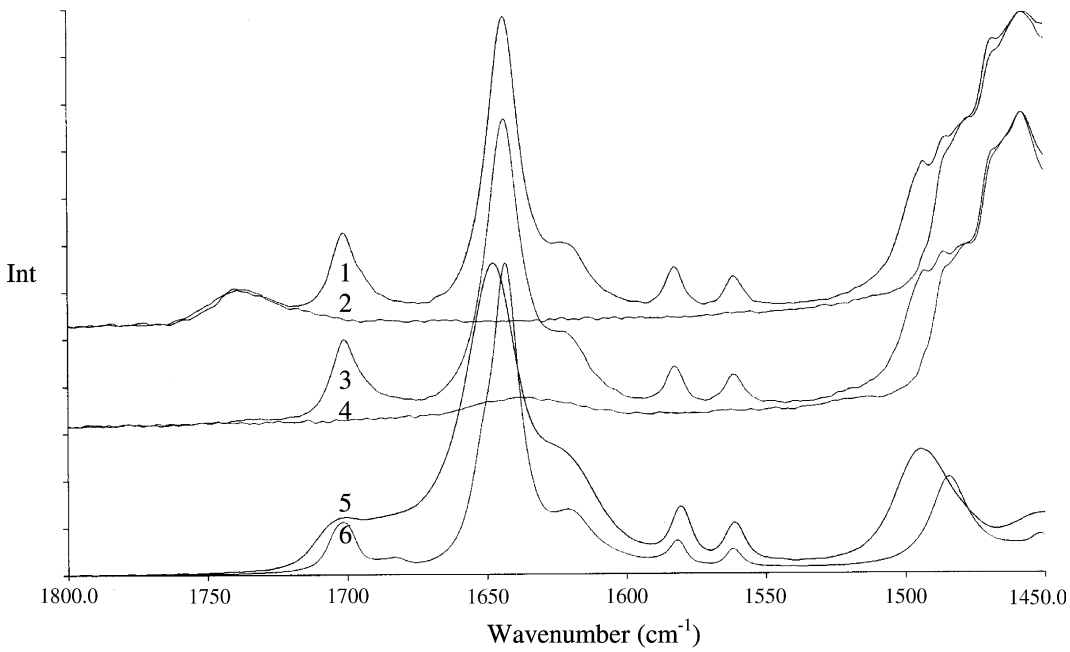

Fig. 2. FT-Raman spectra in the frequency of 1800–1400 cm^{-1}.

is observed. This peak shift was most noticeable at the N–H stretch peak at about 3370 cm^{-1} and at the C=O stretch peak at about 1700 cm^{-1}(Bellamy, 1964).

In our previous study we showed that hydrogen bonding existed between felodipine and all the lipophilic excipients used in this study (Savolainen et al., 2002). However, the total interactions were stronger with cetanol and Precirol® ATO 5 than with stearic acid. In the present study, felodipine demonstrated interactions with both hydrophilic polymers, as the N–H peak shifted to lower frequencies in both the spectra of the melts. Hydrogen bonding is likely to occur between the N–H group of felodipine and O–H group of PEG or Pluronic® F127. However, with PEG 4000, as was also the case with stearic acid (Savolainen et al., 2002), this peak shift in the N–H stretch region was not complete and a double peak could be observed (Fig. 5). The Pluronic® F127 spectra, on the other hand, displayed a complete peak shift in the same region (Fig. 6). This could be interpreted as meaning that there is a greater likelihood of interactions between the less hydrophilic Pluronic® F127 and felodipine than PEG 4000 and felodipine. In both the hydrophilic excipient samples, no significant interactions occurred in the C=O stretch region. The melting process itself could cause the small shifts in the peaks that can be noted in this region. The small changes in the spectra can also be attributed to the possible change in the crystal modification of the drug (Martínez-Ohárriz et al., 1994).

With lipophilic excipients and felodipine, interactions could be observed in both N–H and C=O stretching regions (Savolainen et al., 2002), whereas with the hydrophilic excipients, where interactions only occurred in the N–H stretching region. It can be concluded that the total interactions are greater between felodipine and the lipophilic excipients than between felodipine and hydrophilic excipients. Felodipine is likely to exist as a partial solid solution in all the samples. This assumption is based on the FT-IR and HSM observations. Strong molecular interactions could be noted between felodipine and all of the excipients and,

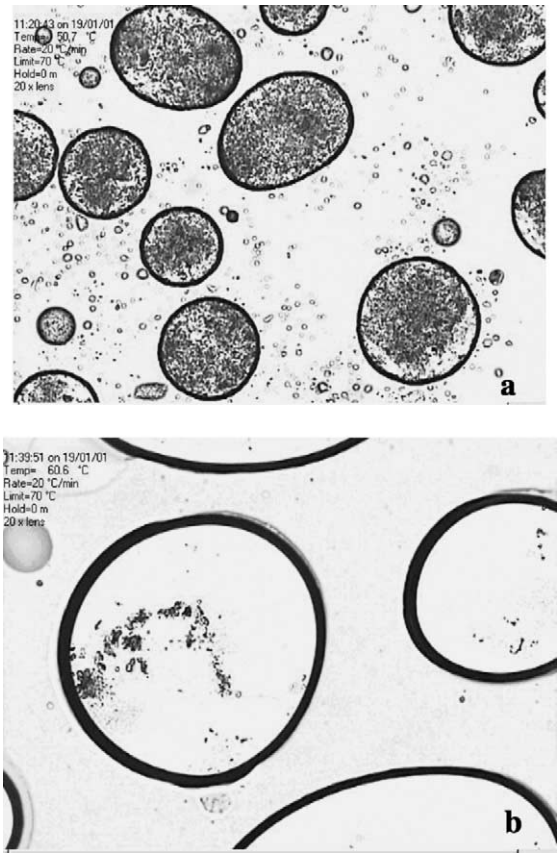

Fig. 3. HSM pictures of felodipine crystals after melting of the excipients: cetanol (a) and cetanol + Pluronic® F127 (b) particles.

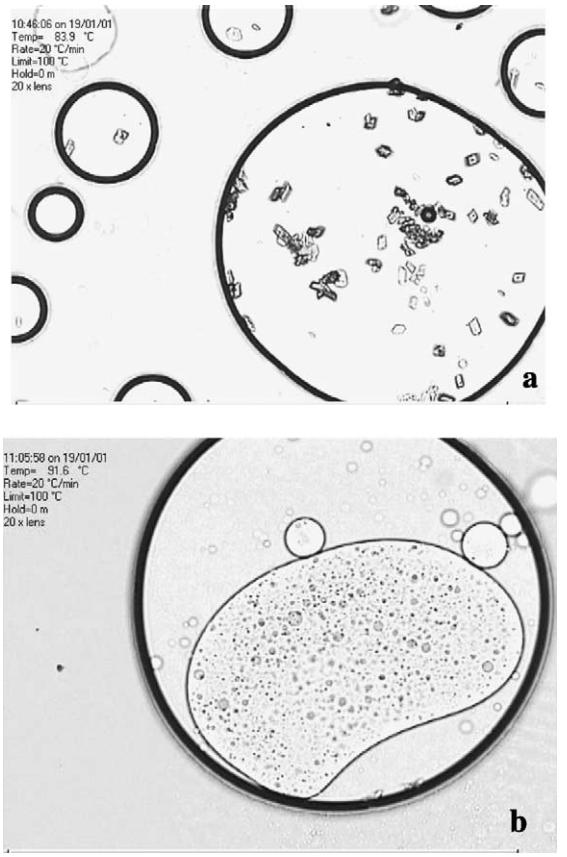

Fig. 4. HSM pictures of felodipine crystals after melting of the excipients: carnauba wax (a) and carnauba wax + Pluronic® F127 (b) particles.

based on the HSM, felodipine crystallinity had decreased.

3.5. Image analysis and SEM

During particle preparation, it was noted that the addition of hydrophilic polymer increased the viscosity of the melt. Changes in viscosity can affect the particle size, morphology and particle size distribution. When the viscosity increases, the droplets that are formed are larger and the solidification process therefore takes longer. If the particles do not have enough time to solidify before they encounter one another or the walls of the vessel, agglomerates will form and the roundness of the particles will decrease.

The median particle size was small in all of the PEG 4000 and Pluronic® F127 samples; the median diameter varied between 20 and 35 μm (Table 3). However, the particle size distribution was wider than when only lipophilic excipient was used as a matrix former. The roundness of the particles was not markedly affected by the addition of the hydrophilic polymer (Table 4). Only when Pluronic® F127 was added to carnauba wax the decrease in the roundness was noticeable. There were more particles, which were fused together compared with the respective samples without the hydrophilic excipient (Fig. 7). The surface of the particles was not as smooth and some holes could be noted in the surface (Fig. 8). In the stearic acid and Precirol® ATO 5 samples, the addition of hydrophilic excipients had no significant effect on the roundness of the particles nor on the surface morphology. The surface was slightly uneven and rough in all of these samples. Like

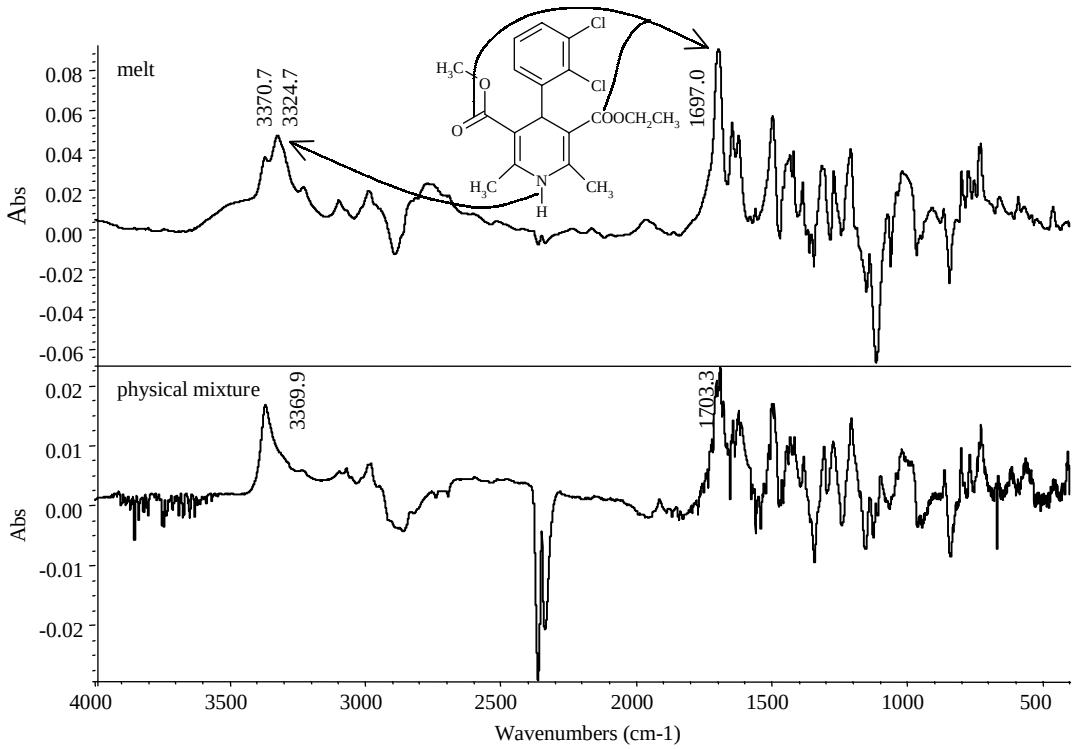

Fig. 5. FT-IR spectra of altered felodipine in the PEG 4000 + felodipine melt and physical mixture.

Table 3
Mean diameter of the number size distribution of the particles[a]

Lipophilic excipient	Hydrophilic excipient	10% fractile (μm)	Median (μm)	90% fractile (μm)
Carnauba wax	–	13.1	29.5	62.9
Carnauba wax	Pluronic® F127	13.9	34.6	97.6
Cetanol	–	13.6	30.3	76.2
Cetanol	PEG 4000	12.7	27.7	78.1
Cetanol	Pluronic® F127	13.1	32.5	76.7
Compritol® 888 ATO	Pluronic® F127	9.5	22.4	51.8
Glyceryl monostearate	Pluronic® F127	9.4	22.3	50.0
Precirol® ATO 5	–	12.2	26.5	64.5
Precirol® ATO 5	Pluronic® F127	11.7	26.8	71.7
Precirol® WL 2155 (experiment 9)	Pluronic® F127	7.9	20.9	49.7
Precirol® WL 2155 (experiment 10)	Pluronic® F127	8.6	23.7	57.3
Stearic acid	–	13.2	28.6	61.8
Stearic acid	PEG 4000	14.0	32.6	76.6
Stearic acid (experiment 6)	Pluronic® F127	12.5	27.6	69.7
Stearic acid (experiment 11)	Pluronic® F127	9.9	24.7	56.3

[a] Results for particles without hydrophilic excipient from Savolainen et al. (2002).

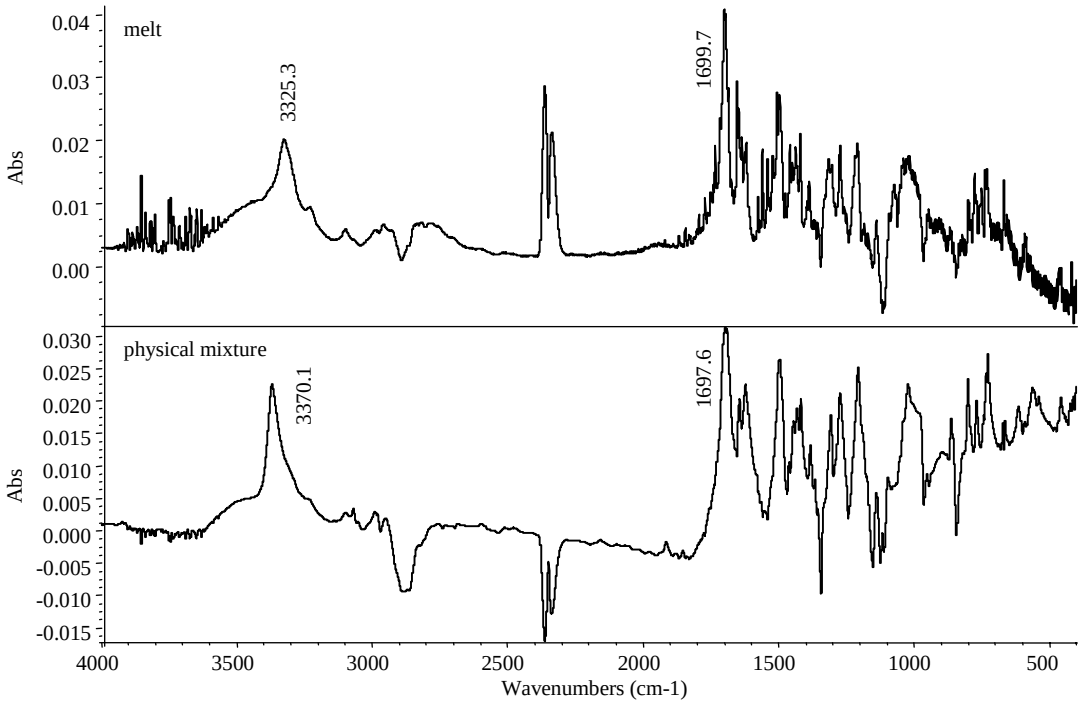

Fig. 6. FT-IR spectra of altered felodipine in the Pluronic® F127 + felodipine melt and physical mixture.

Precirol® ATO 5 also the other glyceride samples were round, when analysed with the image analysis. However, the particles with Precirol® ATO 5 were larger than the other glyceride particles. The microparticles with cetanol were extremely rough and looked crystalline. The addition of PEG 4000 or Pluronic® F127 to the cetanol did not improve the roundness or the surface characteristics of the particles.

Table 4
Roundness of the particles as detected by image analysis[a,b]

Lipophilic excipient	Hydrophilic excipient	10% fractile	Median	90% fractile
Carnauba wax	–	0.714	0.955	0.994
Carnauba wax	Pluronic® F127	0.551	0.891	0.980
Cetanol	–	0.515	0.883	0.974
Cetanol	PEG 4000	0.507	0.845	0.963
Cetanol	Pluronic® F127	0.508	0.871	0.973
Compritol® 888 ATO	Pluronic® F127	0.768	0.970	0.992
Glyceryl monostearate	Pluronic® F127	0.775	0.973	0.994
Precirol® ATO 5	–	0.631	0.924	0.991
Precirol® ATO 5	Pluronic® F127	0.667	0.936	0.992
Precirol® WL 2155 (experiment 9)	Pluronic® F127	0.696	0.932	0.981
Precirol® WL 2155 (experiment 10)	Pluronic® F127	0.612	0.959	0.991
Stearic acid	–	0.693	0.927	0.984
Stearic acid	PEG 4000	0.620	0.931	0.984
Stearic acid (experiment 6)	Pluronic® F127	0.667	0.936	0.988
Stearic acid (experiment 11)	Pluronic® F127	0.692	0.963	0.990

[a] Roundness is a measurement of the length–width relationship, with a value in the range of [0.0, 1.0].
[b] Results for particles without hydrophilic excipient from Savolainen et al. (2002).

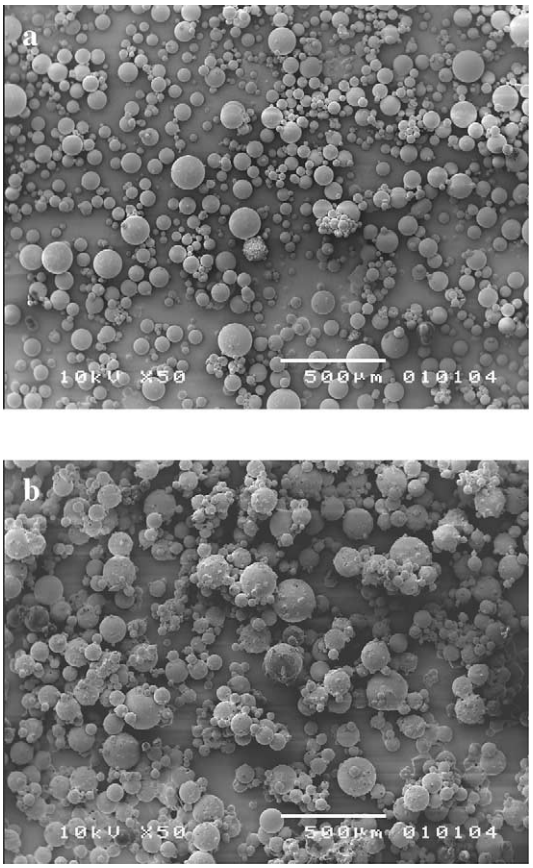

Fig. 7. Scanning electron micrographs of carnauba wax (a), carnauba wax + Pluronic® F127 (b) particles, overall view.

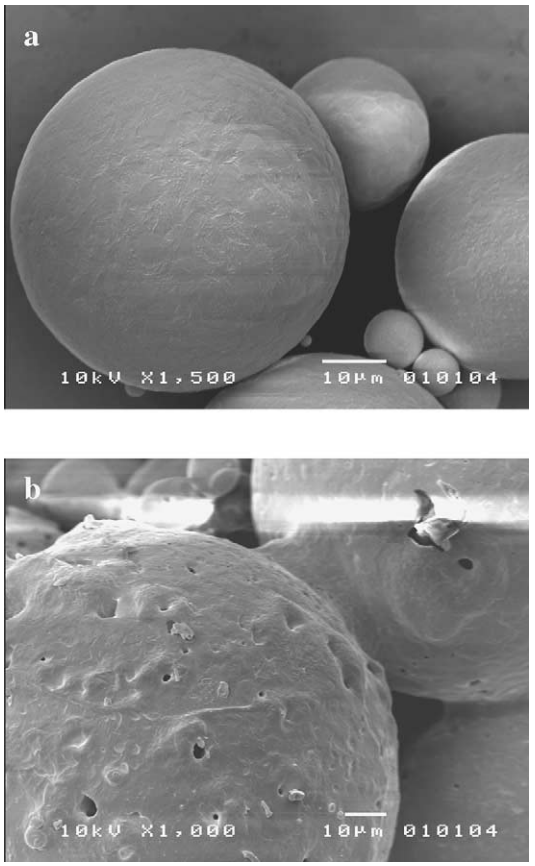

Fig. 8. Scanning electron micrographs of carnauba wax (a), carnauba wax + Pluronic® F127 (b) particle surfaces.

3.6. Dissolution rate

It was assumed that the addition of hydrophilic excipients would increase the dissolution rate, as was the case when mannitol or HPMC was added to Precirol® ATO 5 matrices (Parab et al., 1986). As a more hydrophilic excipient, PEG 4000 would be expected to increase the dissolution rate more than the less hydrophilic Pluronic® F127. The addition of hydrophilic excipient increased the dissolution rate, when carnauba wax (Fig. 9), cetanol (Fig. 10), or Precirol® ATO 5 (Fig. 11) was used as a lipophilic carrier. The effect of hydrophilic excipient was almost negligible in the stearic acid samples (Fig. 12).

Surprisingly, PEG 4000 did not increase the dissolution rate more than the addition of the less hydrophilic Pluronic® F127. In the both cases, where the lipophilic excipient was miscible with both PEG 4000 and Pluronic® F127, the release rate was faster from samples containing Pluronic® F127. From cetanol + Pluronic® F127 tablets, 29% was released after 4 h compared with 12% from cetanol + PEG 4000 tablets. The respective values for stearic acid tablets were 16 and 13%. This can most probably be explained by the solubilizing effect of Pluronic® F127. A similar type of phenomenon has been noted when solid dispersions are prepared using polyoxyethylene 40 stearate and PEG 2000 as carriers (Kaur et al., 1980). The dissolution rates of poorly-soluble drugs were faster, when surface-active polyoxyethylene 40 stearate was used as the carrier. Another possibility is that the faster release of felodipine is related to the stronger molecular

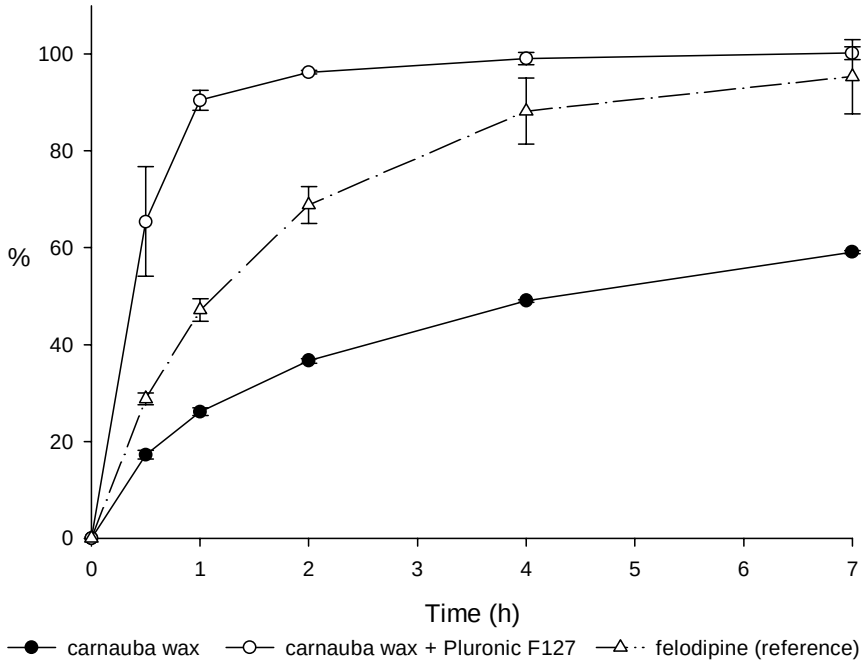

Fig. 9. Dissolution of felodipine from the carnauba wax tablets with a drug content of 10 mg.

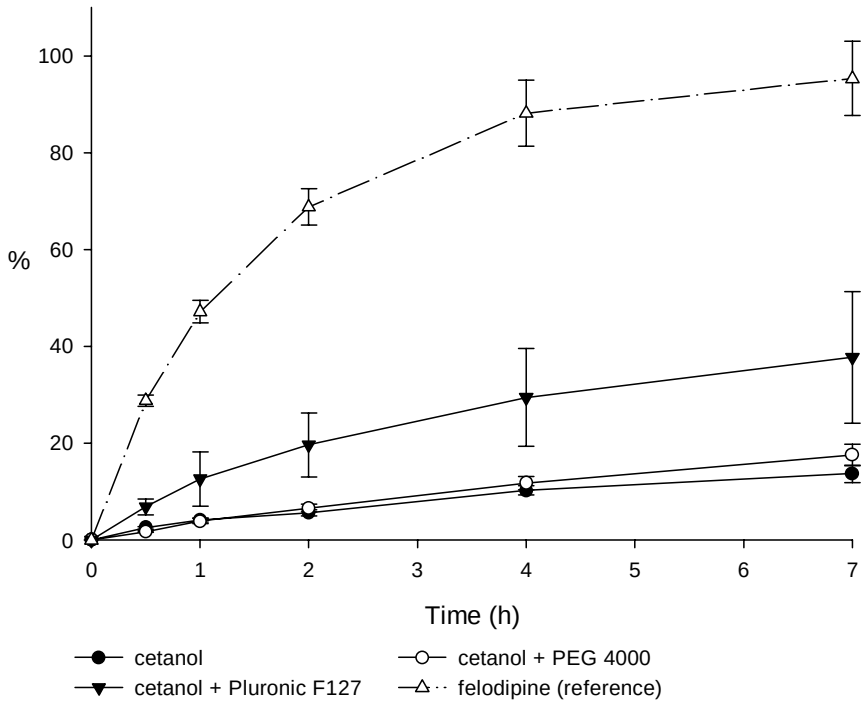

Fig. 10. Dissolution of felodipine from the cetanol tablets with a drug content of 10 mg.

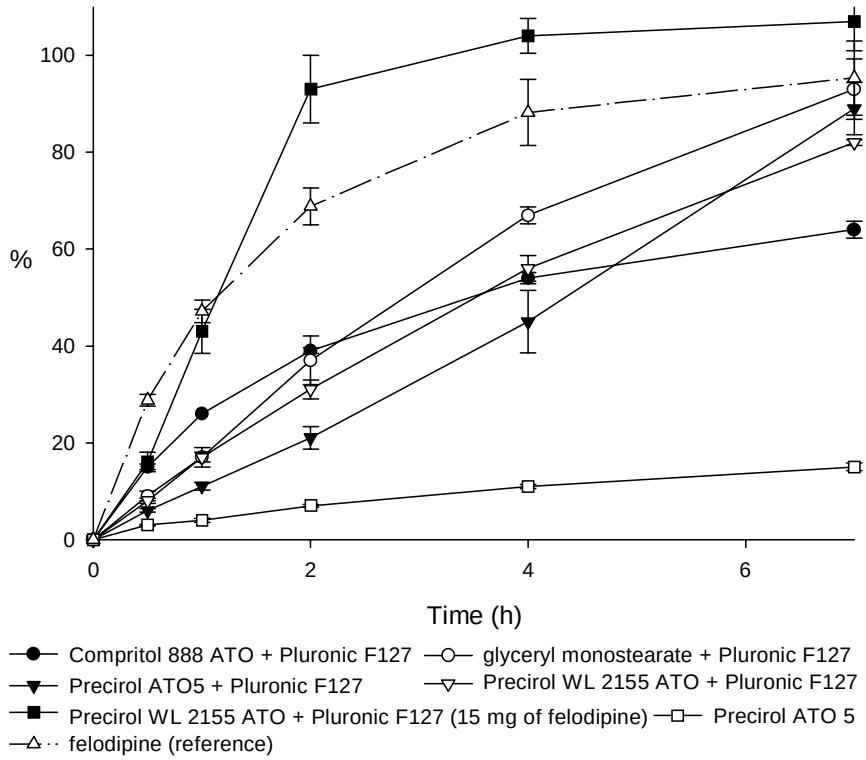

Fig. 11. Dissolution of felodipine from the glyceride tablets with a drug content of 10 mg.

interactions between the drug and Pluronic® F127 compared to the drug and PEG 4000, which were noted with the FT-IR.

The addition of Pluronic® F127 to the cetanol solid dispersion increased felodipine release rate considerably more than PEG 4000 (Fig. 10). As seen in the HSM, there was significantly less crystalline felodipine in the cetanol + Pluronic® F127 sample than in the other cetanol samples. This could explain the notable increase in the dissolution rate. Another explanation may also be the lack of interaction between felodipine and PEG 4000 compared with felodipine and Pluronic® F127, as seen in FT-IR. Stronger interactions with Pluronic® F127 would then lead to a faster release of felodipine from the matrix with the dissolving Pluronic® F127 molecules. The tablet-breaking strength for the mixtures comprising cetanol with Pluronic® F127 was lower (56 N) than when PEG 4000 (85 N) was used. The reduction in tablet hardness may also have contributed to the increase in the dissolution rate by causing the tablets to disintegrate more easily.

According to the HSM, felodipine crystallinity had decreased also in the stearic acid particles with hydrophilic polymers. However, this could not be seen in the dissolution rates. The hydrophilic polymers had hardly any influence to the release rate of felodipine from the tablets with lipophilic excipient–hydrophilic excipient ratio 2:1 (Fig. 12). Stearic acid tablets kept their integrity during the dissolution test and therefore the area exposed to the dissolution medium was significantly smaller than in the other samples. Increasing the amount of hydrophilic excipient Pluronic® F127 to 1:1 in the particles resulted in a faster and zero order release of felodipine.

The addition of Pluronic® F127 to the carnauba wax matrix increased the release rate of felodipine to above that of the reference tablets (Fig. 9). In this case, the solid dispersion functioned as a dissolution enhancer not as a sustained release formulation. Both

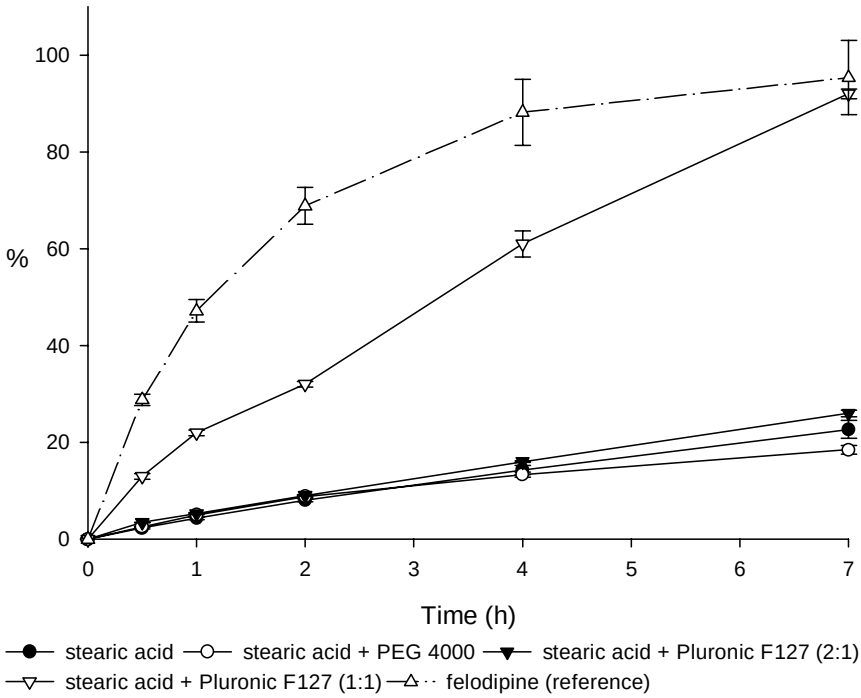

Fig. 12. Dissolution of felodipine from the stearic acid tablets with a drug content of 10 mg.

carnauba wax samples disintegrated easily to particles in the dissolution medium, so the surface area exposed to solvent was too large. Based on the HSM, there was hardly any crystalline felodipine in the carnauba wax + Pluronic® F127 sample. This formulation was thus closest to a true solid solution. Dissolution rate of amorphous felodipine is significantly faster than that of crystalline (Kerč et al., 1991).

Felodipine was released from Precirol® ATO 5-Pluronic® F127 tablets at a constant rate and 45% of the felodipine had dissolved after 4 h (Fig. 11). Constant release rate leads to steady drug levels in plasma, which therefore makes this type of release profile most favourable for felodipine. Based on the results obtained from the pre-tests, a more extensive evaluation on glycerides was made.

As expected, when comparing the felodipine release rates from the glyceride tablets with hydrophilic excipients, the release was slowest from the tablets containing the most lipophilic Compritol® 888 ATO (Fig. 11). Unlike from the other glyceride tablets there appeared to be a burst effect from the Compritol® 888 ATO-Pluronic® F127 tablets.

In comparison, the Precirol® WL 2155 ATO-Pluronic® F127 and glyceryl monostearate-Pluronic® F127 tablets gave faster drug release than Precirol® ATO 5-Pluronic® F127 tablets (Fig. 11). Glyceryl monostearate is less lipophilic (HLB 3.8) than the other glycerides (HLB 2.0). Further, hardness of the glyceryl monostearate-Pluronic® F127 tablets was lower than the Precirol® ATO 5-Pluronic® F127 and Precirol® WL 2155 ATO-Pluronic® F127 tablets, breaking strength of the tablets being 47, 66, and 79 N, respectively. This contributed to fastest drug release from the glyceryl monostearate-Pluronic® F127 tablets compared to the other glyceride tablets containing 10 mg of felodipine. The slightly faster release rate from Precirol® WL 2155 ATO-Pluronic® F127 tablets compared to the Precirol® ATO 5-Pluronic® F127 tablets was possibly caused by the smaller size of the Precirol® WL 2155 ATO-Pluronic® F127 particles. Increasing the amount of drug in the Precirol® WL 2155 ATO-Pluronic® F127 particles (experiment 11, Table 2) resulted in a faster release rate of felodipine as expected.

4. Conclusions

Spray chilling could be used to prepare the microparticles, even though the addition of hydrophilic component increased the amount of agglomerates and widened the particle size distribution. Particles were, however, spherical and in the micrometer domain.

The HSM supported the findings of XRPD, FT-Raman and FT-IR analysis that partial solid solutions were formed in all the samples. FT-IR studies revealed hydrogen bonding between felodipine and all the excipients. The crystallinity of felodipine had decreased in all the samples, even though the amount of crystalline felodipine varied significantly depending on the composition of the matrix. The closest to a true solid solution was the carnauba wax + Pluronic® F127 composition.

Addition of hydrophilic excipient could be used to adjust the dissolution rate. Pluronic® F127 appeared to have a solubilizing effect on the felodipine and therefore increased the dissolution rate more than PEG 4000. Also the molecular interactions between felodipine and Pluronic® F127 were stronger than between felodipine and PEG 4000. From the carnauba wax + Pluronic® F127 tablets, which were closest to a true solid solution, felodipine was released faster than from the reference tablets. The most promising dissolution pattern was obtained when glycerides were used as matrix materials for controlled-release tablets; e.g. from Precirol® ATO 5 + Pluronic® F127 tablets a zero order release was obtained and 45% of the felodipine was released after 4 h.

Combining lipids and hydrophilic polymers in the molten state to form solid dispersion microparticles offers a promising method to produce a controlled-release formulation. However, the long-term stability of these solid dispersions should be studied to determine whether the noted molecular interactions are strong enough to maintain the solid state of the drug.

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