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Evaluation of controlled-release polar lipid microparticles

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Abstract

The aim of the present study was to prepare controlled-release tablets of poorly-soluble drug, felodipine, and various erodable lipophilic excipients. Spray chilling was used to formulate the drug and the excipients into solid dispersion microparticles, which were then compressed. The microparticles were characterised by Fourier transform infrared spectroscopy, hot-stage microscopy, scanning electron microscopy, and image analysis. The amine and the carbonyl groups of felodipine formed hydrogen bonds with the carriers. The shape of the particles was spherical with the median particle diameter ranging from 25 to 35 μm. Surprisingly, the degree of crystallinity in felodipine and the ease of tablet disintegration played a more significant role on the felodipine dissolution rate than the matrix lipophilicity. Felodipine release rate was slowest from the least lipophilic tablets.

Keywords: Controlled release; Felodipine; Microparticles; Polar lipids; Solid dispersion; Spray chilling

1. Introduction

Controlled release is usually accomplished using a membrane or matrix. Matrix type formulations are prepared from either swellable hydrophilic polymers or non-swellable lipophilic excipients, like waxes and fats. From the polymer matrices, the drug release rate is controlled by the diffusion of drug molecules in the swollen polymer matrix (Colombo et al., 2000). That is why drug solubility in the matrix material has a marked influence on the release rate. This might create problems, when the drug is very hydrophobic, as is often the case with new drug molecules. When lipophilic materials are used as a matrix, this problem relating to poor drug solubility in the matrix can be avoided.

When a non-swellable lipophilic excipient is used as a matrix material in controlled-release formulations, the drug substance and the excipient have to be formulated into a solid dispersion; just mixing the ingredients is not enough. Malamataris et al. (1991) showed that satisfactory release rate retardation was not attained when tablets were prepared from a physical mixture of model drug, palmitostearate and different direct compression excipients. Drug release, on the other hand, could be prolonged from a solid dispersion matrix, where

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the physical mixture of drug and wax was first melted and then granulated through a sieve.

Solid dispersion technique is commonly used to increase solubility of poorly water-soluble drugs. The concept of solid dispersion covers a wide range of systems (Chiou and Riegelman, 1971). The enhancement in the dissolution rate is obtained by one or a combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wettability due to close contact with a hydrophilic carrier, precipitation as a metastable crystalline form or a decrease in substance crystallinity. The type of solid dispersion formed depends on both the carrier–drug combination and the method of manufacture (Serajuddin, 1999).

In spray chilling or spray congealing, as it is also called, the melted mass is atomised into droplets, which quickly solidify in cool air (Killeen, 1993). The advantage in spray chilling is that no additional manufacturing step is needed to pulverise the solid dispersion. In pharmacy, spray chilling has been used to prepare sustained-release formulations (Cusimano and Becker, 1968; Akiyama et al., 1993; Rodriguez et al., 1999), improving stability (Schwendeman et al., 1998) and taste masking (Yajima et al., 1999). The method has also been used by the food industry, for example, to encapsulate vitamins and minerals (Gibbs et al., 1999).

The aim of this study was to produce controlled release-tablets of the poorly-soluble model drug substance, felodipine [ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate], using various lipophilic excipients as carriers. Before compression, the spray chilling technique was used to prepare a solid dispersion of the drug and the lipophilic excipients. Felodipine was chosen as a model drug substance, because it is not temperature sensitive and it is poorly soluble in water. The lipophilic materials chosen as carriers were all erodable polar lipids. Their melting points were between 50 and 90 °C, which made them suitable to use in the spray chilling process.

One of the major problems concerning the use of solid dispersions is their stability. If the molecular interactions between the drug and the excipient are not strong enough to keep the drug in an amorphous state or in a metastable crystalline form, the drug tends to transform back to a stable crystalline form (Frömming and Hosemann, 1985). These changes affect the chemical and physical properties of the formulation, e.g. dissolution rate of the drug. Therefore, the solid state of felodipine in the solid dispersions and the type of interactions that occur between felodipine and the excipients were also studied.

2. Materials and methods

2.1. Materials

Felodipine was obtained from AstraZeneca (Sweden). Each lipophilic excipient represented a different group 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), stearic acid and carnauba wax were purchased from Condea Chemie GmbH (Germany), Scharlau Chemie S.A. (Spain) and Frank B. Ross (USA), respectively. Cutina® HR and Precirol® ATO 5 were obtained as a gift from Cognis GmbH (Germany) and Gattefosse (France), respectively. Microcrystalline cellulose (Avicel® PH101, FMC International, Ireland) was used as a tablet diluent and sodium stearyl fumarate (MOEHS, Spain) as a glidant.

Table 1
Classification of the lipophilic excipients

Category	Lipid	Description
Fatty alcohol	Cetanol	Cetyl alcohol, C16 alcohol
Fatty acid	Stearic acid	C18 acid
Fatty acid ester	Precirol® ATO 5	Glyceryl palmitostearate
Hydrogenated fatty acid ester	Cutina® HR	Hydrogenated castor oil
Polar wax	Carnauba wax	A complex mixture containing e.g. esters of acids and hydroxyacids

2.2. Preparation of microparticles

In spray chilling technique, lipophilic material was melted at 110 °C and felodipine was dissolved into it. The weight ratio of the drug to the lipophilic excipient was 1:4 (w/w). 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

Lipophilic material was melted at 110 °C (120 °C, when carnauba wax was used). Drug substance was then added to the melt. The weight ratio of the drug to the lipophilic excipient was 1:4 (w/w). After felodipine had dissolved, 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. The samples were stored in a desiccator.

2.4. Preparation of physical mixtures

For comparison, physical mixtures were prepared for FT-IR analysis from felodipine and lipophilic excipients in weight ratio 1:4 (w/w). Both the lipophilic excipient and felodipine were sieved through a 350 μm sieve. Cetanol, which was in the form of flakes, was first ground in a mortar. The sieved excipient was then mixed with sieved felodipine. The samples were stored in a desiccator.

2.5. Preparation of tablets

All the microparticle samples were compressed into tablets, which had a theoretical felodipine content of 10 mg. Microcrystalline cellulose (Avicel® PH101) was added as a tablet diluent. The tablet weight was 200 mg. Reference tablets containing 10 mg felodipine and 190 mg microcrystalline cellulose 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 mixer (Turbula 72C, Willy A Bachofen AG, Switzerland) for 10 min. The tablet mass for each tablet was weighed separately and compressed with an eccentric tablet press (Kilian SP300, Kilian & Co GmbH, Germany) 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 4M, Dr. Schleuniger Productronic AG, Switzerland). Therefore, the upper and lower punch distance was varied from 1.05 to 2.25 mm to control the tablet hardness. Before further analysis, the samples were stored in a desiccator in room temperature.

2.6. Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectroscopy was used to detect the existence of interactions between felodipine and lipophilic excipients in the melted samples. Carnauba wax sample was not studied, since the exact composition of the excipient is unknown. This would make the interpretation of the spectra difficult. The infrared spectra of the samples were obtained on a Fourier transform infrared spectrometer (Nicolet Nexus™ 870 FT-IR, Nicolet Instrument Co, USA). The samples were first ground gently in a mortar, if necessary, and mixed with KBr before being compressed into tablets. The samples were scanned 50 times. The FT-IR spectrometer had a nitrogen purge. In order to obtain a better idea of the possible interactions, the spectra were subtracted. The spectra (S) of the melted or powdered excipient were subtracted

from the spectra of a binary solidified melt or physical mixture respectively according to following example:

$$[S_{\text{stearic acid + felodipine melt}}] - [S_{\text{stearic acid melt}}] = [S_{\text{altered felodipine}}]_1$$

$$[S_{\text{stearic acid + felodipine physical mixture}}] - [S_{\text{stearic acid}}] = [S_{\text{altered felodipine}}]_2$$

The CH_2 stretching peak at 2926 ± 10 and 2853 ± 10 cm^{-1} (Bellamy, 1964) was used as the internal standard in all the samples, as it did not appear in the felodipine spectra and it was not expected to be involved in any interactions.

2.7. 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 of storage. 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., Japan) before characterisation with SEM. The current used for sputtering was 10 mA and the sputtering gas was argon.

2.8. Image analysis

Information about the particle size distribution and the roundness of the particles was obtained using an image analysis system (BeadCheck™ 830, Pharma Vision Systems AB, Sweden). From each batch, 5000 particles were analysed.

2.9. Hot-stage microscopy (HSM)

The spray-chilled particle samples 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 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 carriers melted at lower temperature, crystalline felodipine could be seen in the microscope if felodipine and the excipient had not formed a solid solution.

2.10. Felodipine content of tablets

The analysis was performed using high performance liquid chromatography (HPLC) (Waters 717 plus autosampler, Waters Co., USA; Perkin Elmer pump 200, Perkin Elmer Co., USA; Chrompack UV-VIS detector, Netherlands) about one and a half months after the particles were manufactured. A C_{18} column (NOVA PAK™) with d_p 5 μm and dimensions 4.6×150 mm, was used. Absorbance was measured at 362 nm.

To extract the felodipine from the tablets, ten tablets were pulverised. Precisely weighed amounts of tablet powder were dissolved into a mixture of methanol, acetonitrile and sodium dihydrogen phosphate buffer (pH 3.0) (1:2:2 v/v/v). The mixtures were kept in an ultrasonic bath. The solution was centrifuged for 15 min at 4000 rpm and filtered through a 0.5 μm filter before the HPLC analysis. Samples were made in duplicate.

2.11. Dissolution

The rate of drug release of tablets was tested using the USP II paddle method about one and a half months after particle preparation. The dissolution test from each batch was performed in triplicate. Dissolution test was performed in a dissolution medium of 500 ml of sodium dihydrogen phosphate buffer at pH 6.5. An amount of 2.0 g of cetyl trimethylammonium bromide was added to the buffer to increase the solubility of felodipine and to preserve sink conditions during dissolution. The measurements were carried out at 37 °C and the paddle was rotated at 100 rpm. Each tablet was

placed in a basket located about 1 cm above the paddle. Aliquots (10 ml) were withdrawn after 0.5, 1, 2, 4 and 7 h and filtered through a 1.2 μm filter.

The filtrated sample solutions were then analysed using a UV spectrophotometer (Perkin Elmer UV/VIS spectrophotometer Lambda 14, Perkin Elmer Co., USA) at wavelengths of 362 and 450 nm. Due to small turbidity in the sample solutions after filtration, a background correction to the absorbance (A) was made:

$$A(t) = A_{362}(t) - A_{450}(t).$$

3. Results and discussion

3.1. FT-IR spectroscopy

When hydrogen bonding occurs between felodipine and the excipient, a shift in certain peaks, which are affected by an interaction, can be observed in the felodipine spectra. In felodipine, the groups in which hydrogen bonding can occur are the amine group in the ring and the two carbonyl groups (Fig. 1). When hydrogen bonding occurs, bond energy at the N–H or C=O bond decreases and a peak shift to lower frequencies is observed. This peak shift was most noticeable at the N–H stretch peak at 3370 cm^{-1} and at the C=O stretch peak at 1699 cm^{-1} (Fig. 1). A decrease in the N–H bond energy, on the other hand, increases the C=N bond energy at the ring. This was observed in the N=C stretch peak at 1496 cm^{-1}, which shifted to higher frequencies.

It could be seen from the subtraction spectra representing the modified drug that some degree of interaction existed between felodipine and the lipophilic excipient in all the melt samples. A shift could be seen in the C=O stretching peak and the N=C stretching peak. However, these samples differed from one another with regard to the N–H stretching peak.

Two types of change could be seen. A clear shift in the N–H peak was noted from 3372.7 to 3338.9 cm^{-1} in the cetanol melt sample and from 3371.4 to 3338.5 cm^{-1} in the Precirol® ATO 5 melt sample (Fig. 2). This shift is not observed in the physical mixture (Fig. 2, bottom). Water in the sample gives rise to the broad shoulder in the physical mixture sample. In the stearic acid and Cutina® HR samples, a double peak may be noticed in the N–H stretch region in the melted samples (Fig. 3). This doublet probably reflects

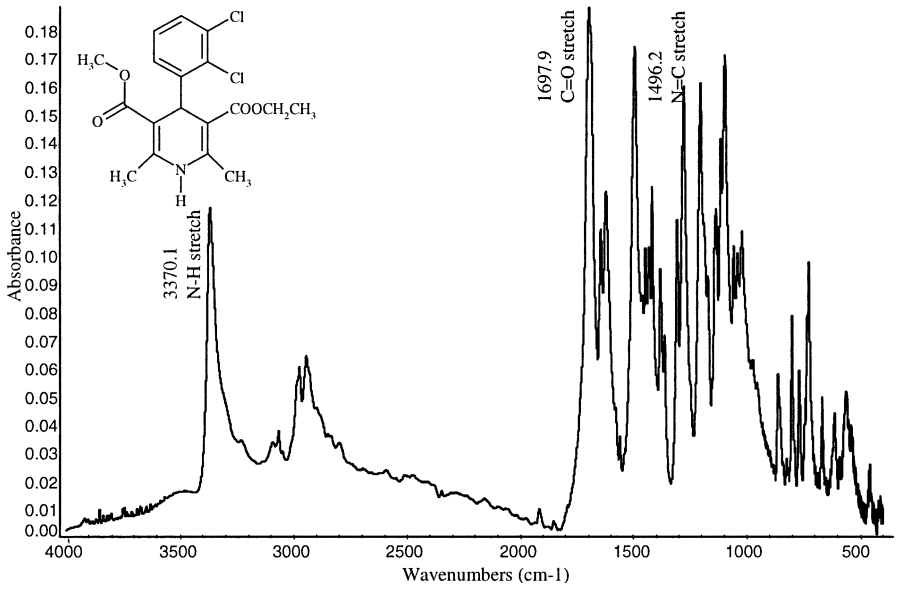

Fig. 1. The structural formula and the FT-IR spectra of felodipine.

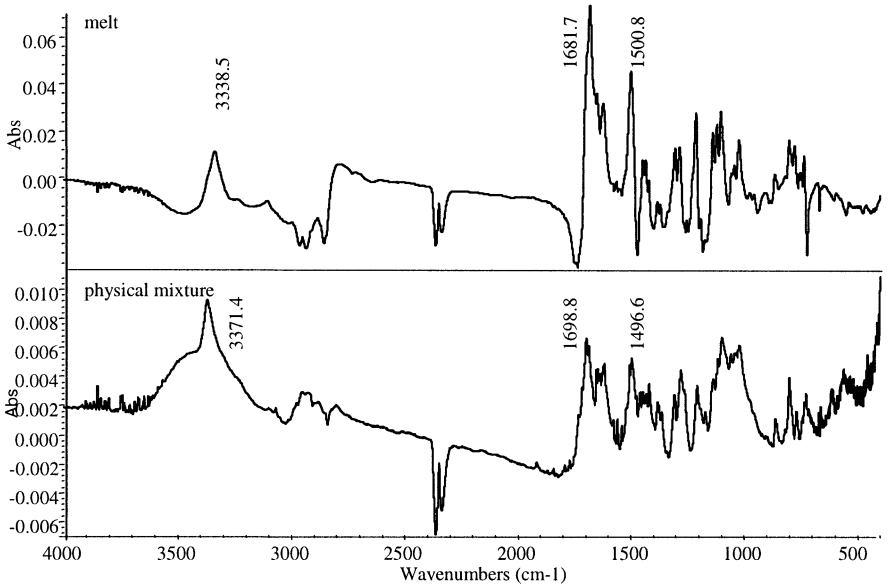

Fig. 2. FT-IR spectra of altered felodipine in the Precirol® ATO 5+felodipine melt and physical mixture.

N–H groups that have interacted as well as those that show no interactions and which thus show no decrease in the bond energy. Stearic acid, for example, has a tendency to form dimers (Bellamy, 1964). This competitive reaction could hamper the formation of hydrogen bonds between felodipine and stearic acid. If most of the stearic acid exists as dimers, there may not be enough free C=O-groups to react with all the felodipine molecules. This may explain the double peaks in the N–H stretch region. On the basis of the observed spectra, the amine group of felodipine is less likely to form

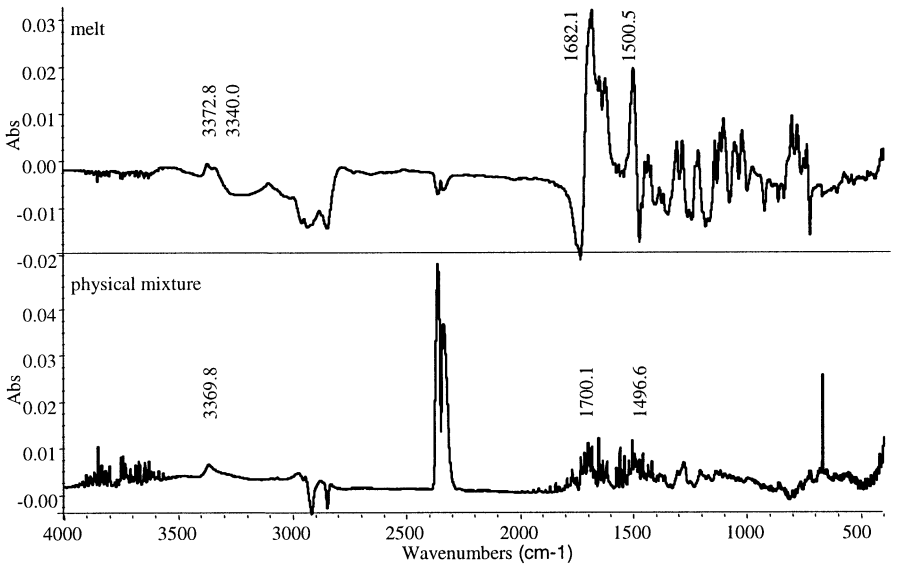

Fig. 3. FT-IR spectra of altered felodipine in the Cutina® HR+felodipine melt and physical mixture.

hydrogen bonds, when stearic acid or Cutina® HR is used than when cetanol or Precirol® ATO 5 is used. There are therefore indications that the total interaction that occurs between felodipine and the excipient is weaker, when stearic acid or Cutina® HR is used.

3.2. Image analysis and SEM

Number particle size distribution was very similar in all the samples; the median particle diameter varied from 26.5 to 30.3 μm (Table 2). There was, on the other hand, variation in the surface morphology of the particles. Carnauba wax particles, which were roundest and had the smoothest surface of all the samples in SEM (Fig. 4a), were also the roundest according to the image analysis (Table 3). The surface of Cutina® HR (Fig. 4b) and Precirol® ATO 5 (Fig. 4c) particles was also quite spherical and smooth. Their roundness as detected by the image analysis was, however, not quite as good (Table 3). Since both samples had more agglomerates than the carnauba wax sample, it is possible that, even though the software program is supposed to separate agglomerated particles before analysis, not all the particles were separated. The agglomerates would therefore affect the result.

Stearic acid particles had imperfections on their surfaces although the particles were somewhat spherical (Fig. 5a). Cetanol particles, on the other hand, had a roundness of 0.88 and the surface of the particles was extremely rough and looked crystalline in SEM (Fig. 5b). These findings agreed with the findings of Rodriguez et al. (1999), who used an ultrasonic atomiser for the spray chilling of carnauba wax, Cutina® HR and stearic acid. They also found that all the particles were spherically shaped, although there were imperfections on the surface of the stearic acid particles. Carnauba wax and Cutina® HR particles, on the other hand, had perfectly smooth surfaces.

3.3. HSM

Hot-stage microscopy (HSM) is often combined with differential scanning calorimetry to characterise the solid-state form of the drug in solid dispersions (Ginés et al., 1995; Vélaz et al., 1998). HSM analysis of cinnarizine-Gelucire® 53/10 solid dispersions showed that cinnarizine took the form of microcrystalline particles in the formulation (Ginés et al., 1995). The HSM 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 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. There appeared to be more crystalline felodipine in the cetanol (Fig. 6a), Precirol® ATO 5 and stearic acid samples compared with the carnauba wax (Fig. 6b), and Cutina® HR samples. It should be noted, however, that the expected correlation between the amorphicity of the samples and the interactions detected by FT-IR did not exist. Some degree of interactions was, however, noted in all the samples. This will be studied in the future by X-ray powder diffractometry.

Table 2
Particle size distribution

Lipophilic excipient	10% fractile (μm)	Median (μm)	90% fractile (μm)
Carnauba wax	13.1	29.5	62.9
Cetanol	13.6	30.3	76.2
Cutina® HR	12.2	29.7	72.1
Precirol® ATO 5	12.2	26.5	64.5
Stearic acid	13.2	28.6	61.8

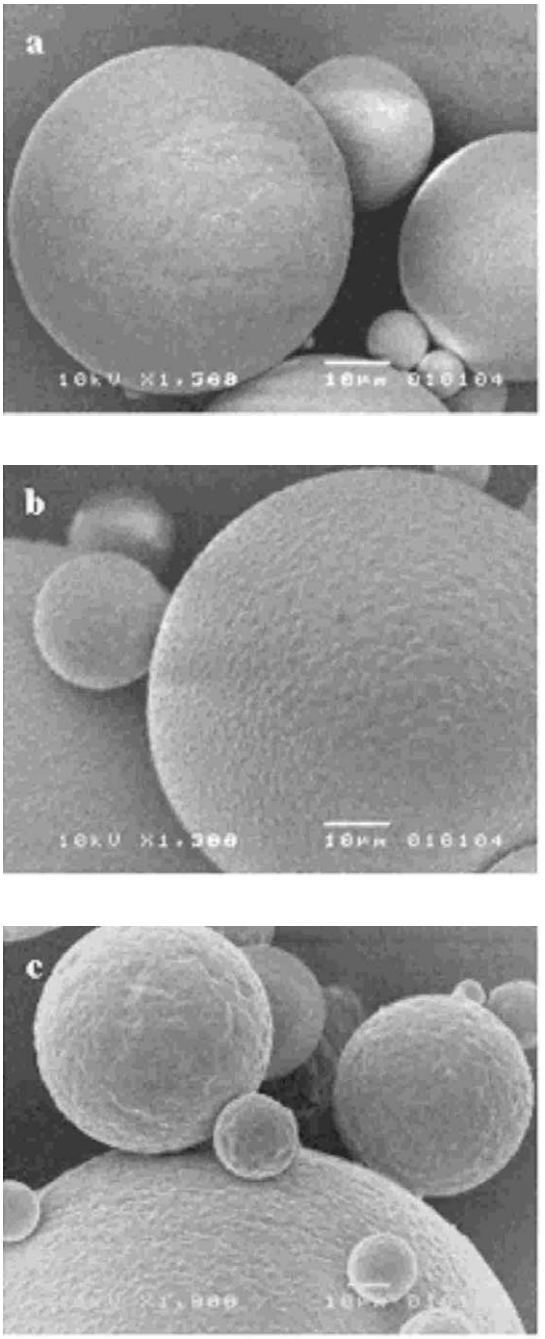

Fig. 4. Scanning electron microphotographs of carnauba wax (a), Cutina® HR (b), and Precirol® ATO 5 (c) particle surfaces.

Table 3
Roundness of the particles as detected by image analysis[a]

Lipophilic excipient	10% fractile	Median	90% fractile
Carnauba wax	0.714	0.955	0.994
Cetanol	0.515	0.883	0.974
Cutina® HR	0.522	0.909	0.991
Precirol® ATO 5	0.631	0.924	0.991
Stearic acid	0.693	0.927	0.984

[a] Roundness is a measurement of the length-width relationship, with a value in the range of [0.0, 1.0].

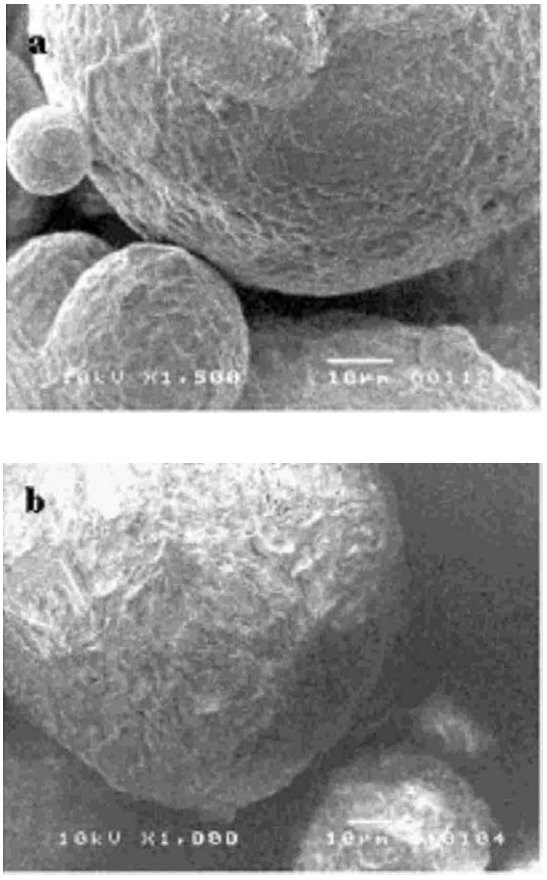

Fig. 5. Scanning electron microphotographs of stearic acid (a), and cetanol (b) particle surfaces.

3.4. Dissolution

Drug release from lipid particles is affected by several factors, e.g. particle size, drug content, lipophilic excipient, and dissolution medium. The

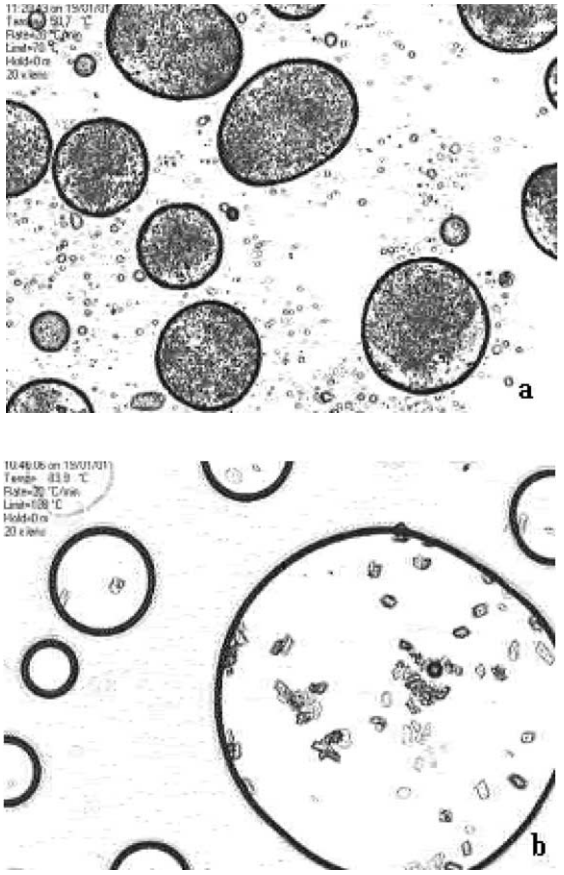

Fig. 6. HSM pictures of felodipine crystals after melting of the excipients: cetanol (a) and carnauba wax (b) particles.

most important one, however, is the lipophilic excipient itself (Cusimano and Becker, 1968; Akiyama et al., 1993). The drug release is expected to be slower from more lipophilic matrices. When studying theophylline release from spray-chilled stearic acid and carnauba wax particles for example, Akiyama et al. (1993), Rodriguez et al. (1999) noted that theophylline is released more rapidly from the less lipophilic stearic acid particles than from carnauba wax. Carnauba wax is known to solidify as a metastable form during the spray-chilling process and to change to a thermodynamically-stable form during storage (Emås and Nyqvist, 2000). Changes could already be seen after 1 month of storage. Changes in the polymorphic form of the carrier could also affect the release rate of the drug. As expected, lipophilic carrier prolonged felodipine release from the tablets. However, contrary to the studies of Akiyama et al. (1993), Rodriguez et al. (1999), drug release was slower from stearic acid (less lipophilic) than carnauba wax tablets. Therefore, the release rate was not merely regulated by the lipophilicity of the wax (Fig. 7).

Three types of release rate profile could be noted. From stearic acid, cetanol and Precirol® ATO 5 matrices, felodipine was released slowly; less than 25% had dissolved after 7 h. The crystallinity of the cetanol particles, as seen in SEM, may have contributed to the surprisingly slow dissolution rate from the cetanol tablets. Carnauba wax had a moderate effect on the release rate, 62% had dissolved after 7 h. Cutina® HR, on the other hand, had almost no effect on the felodipine dissolution rate. The release rate profile was quite similar to that of felodipine reference tablets. After 1 h, more than 40% of felodipine had dissolved.

The fast release from the Cutina® HR and the relatively fast release from the carnauba wax tablets cannot be explained by the hydrophilicity of the components. Both are very lipophilic. These tablets disintegrated easily during dissolution and no capping could be seen, as was the case with most of the other samples. The surface area exposed to the dissolution medium was therefore larger and the dissolution rate was faster. Car-

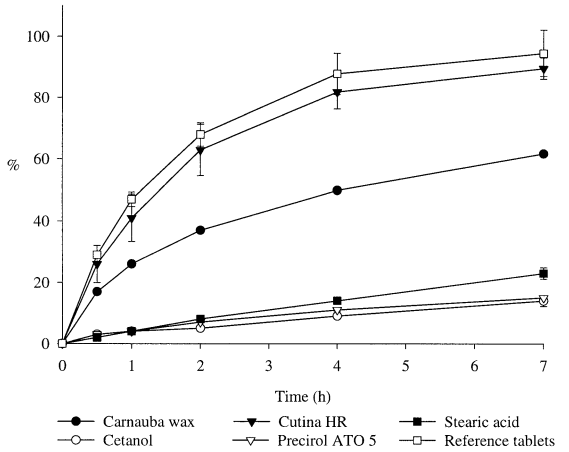

Fig. 7. Comparison of felodipine dissolution rates from different lipophilic matrices.

nauba wax and Cutina® HR have higher melting temperatures, over 80 °C, than the other excipients, which have melting temperatures closer to 50 °C. During compression, heat is always formed. It is possible in the case of particles with lower melting temperatures that enough heat is formed to partly melt the particles at the surface of the tablet. This would explain the capping phenomenon during dissolution. Ketolainen et al. (1993) have studied the temperature changes that occur during the tabletting of microcrystalline cellulose (Avicel® PH 102). The most significant temperature rise was noted on the upper and lower surfaces (6–9 °C). The temperature distribution on the surfaces was not, however, even and, at some locations; the temperature rose considerably more than 6–9 °C. The high-pressure conditions created during compression can also cause the wax matrix to melt at temperatures lower than the normal melting point. The high pressure created during extrusion caused the carnauba wax to melt at 70 °C (Miyagawa et al., 1996). The normal melting temperature of carnauba wax is around 80–86 °C.

On the other hand, based on the HSM, the carnauba wax and Cutina® HR particles appeared to have more amorphous felodipine in them than the particles prepared from other excipients. Amorphous material dissolves more rapidly than crystalline material and it is probable that this has also caused the increase in the dissolution rate.

4. Conclusions

Spray chilling was used to prepare solid dispersion microparticles of felodipine and various polar lipids. To obtain a feasible dosage form the particles were compressed. Unexpectedly, the degree of felodipine crystallinity and the ease of tablet disintegration played a more significant role on the drug release rate than the matrix lipophilicity. The felodipine release rate was extremely slow from the least lipophilic cetanol and stearic acid tablets, less than 15% was released after 4 h. Equally low dissolution rate was obtained from the Precirol ATO 5 tablets. Felodipine was released markedly faster from the most lipophilic but easily disintegrating carnauba wax tablets; 50% had dissolved after 4 h. From Cutina® HR tablets, which also disintegrated easily, dissolution could not be prolonged at all. Based on the HSM, these two tablet samples, carnauba wax and Cutina® HR, also had the least crystalline felodipine.

Spray chilling proved to be a suitable method for manufacturing solid dispersion microparticles from lipids of different types. The sprayed particles were round and in the micrometer domain in all the samples. The surface morphology of the particles varied greatly depending on the excipients that were used.

Amorphous material tends to change to a more stable polymorph during storage. However, the noted hydrogen bonding between the drug and the excipients has a stabilising effect on the solid dispersions. This might hinder the phase transitions to a more stable polymorph. Therefore, the long-term stability of these felodipine particles should be studied.

In the future, adjusting the felodipine release rate by using a combination of a hydrophilic excipient with the lipids will be studied. Also, the solid state of the drug in the samples will be determined by powder XRD. In addition, the significance of the drug content and the particle size should be studied.

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