# PHARMACEUTICAL TECHNOLOGY

# Pair Distribution Function X-Ray Analysis Explains Dissolution Characteristics of Felodipine Melt Extrusion Products

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**ABSTRACT:** Solid solutions of felodipine with EUDRAGIT® E and EUDRAGIT® E/NE were shown to dramatically increase the dissolution rate of felodipine in biorelevant media. Of the two polymer systems, extrudates containing 5% EUDRAGIT® NE showed a faster dissolution rate and less recrystallization (no precipitation within 2 h). Although differential scanning calorimetry (DSC) and conventional X-ray powder diffraction (XRPD) were able to verify the amorphous state of the drug after melt extrusion, it was not possible to differentiate the two extrudate compositions further with these methods. We then applied pair distribution function (PDF) analysis to investigate extrudates. It was possible to more closely characterize the solid state of the amorphous extrudates in terms of local structural order: PDF analysis revealed that addition of minor amounts of EUDRAGIT® NE to the main component EUDRAGIT® E during extrusion changed the local structure of EUDRAGIT® E in a nonadditive way. We conclude that local ordering can be important to the release characteristics of extrudates, even when the components are present in the amorphous state. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:1476–1486, 2009

**Keywords:** amorphous; dissolution; glass transition; solid dispersion; solid solutions; extrusion; solubility

## INTRODUCTION

Many potential drug candidates are poorly soluble, often resulting in poor and variable oral bioavailability.[1] Finding strategies to increase the dissolution rate of poorly soluble drugs is, in fact currently one of the greatest challenges in formulation development.

Various techniques have been used to improve the solubility of poorly soluble drugs including chemical modifications of the drug (e.g. salt formation,[2] soluble prodrugs[3]) and physical modifications like particle size reduction (micronization,[4] nanosizing[5]), modification of the polymorphic

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form or the crystal habit,[6] complexation with cyclodextrins,[7] solubilization[8] and self-emulsifying drug delivery systems.[9]

Another widely examined possibility is the preparation of drug dispersions in carriers resulting in either solid dispersions (nonmolecular dispersion of drug in carrier), eutectic mixtures or solid solutions (molecular dispersion of drug in carrier, one-phase system).[10]

Numerous studies on preparation of solid dispersions have been published using different methods such as spray-drying,[11] freeze-drying,[12] cogrinding[13] and solvent evaporation.[14]

Recently, melt extrusion has been used to form solid solutions of poorly soluble drugs[15] in a carrier in order to achieve large increases in dissolution rate. Melt extrusion offers many advantages compared to other techniques. It is a continuous, one-step process, which can be controlled well. Since organic solvents are not required to dissolve the drug and carrier, toxicological and environmental risks are minimized and the process is cost-effective. The resulting product is an amorphous solid dispersion of the drug in the polymer. One issue with the formation of disperse systems by melt extrusion (as with other methods) is the characterization of the physical state. Small regions of aggregation or ordering which cannot be detected by conventional methods (e.g. X-ray diffraction or DSC), can lead to physical instability of the formulation over time, with profound, adverse effects on the release behavior. Methods are therefore sorely needed to detect local ordering (on the nm scale) as early and accurately as possible in the formulation screening stage of development.

In the last years, analysis of the atomic pair distribution function (PDF), obtained from total scattering X-ray powder diffraction data by Fourier transformation, has been further developed to gain detailed insight into the local structure[16] and provide a fingerprint of the interatomic distances that define a particular solid form.[17,18] Since the degree of crystallinity is irrelevant to the method, PDF may be applied to glasses as well as to perfect crystals and any state in between. It thus is a method to extract more detailed information from X-ray powder diffraction results that would usually lead to simply designating the product as "poorly crystalline" or "amorphous."

The PDF displays the probability of finding atoms at a certain distance from another. Since the PDF from X-ray data is the sum over all distances—weighted by the atomic number—even larger structural entities or domains of the same local structure will be visible if they are ordered in some way. Note that the PDF is referenced to an average density, that is, negative (positive) peaks mean less (more) frequent distances for pairs of atoms than the average. Recently, PDF has been implemented in the pharmaceutical field, for example to characterize the amorphous form of indomethacin prepared by cryogrinding crystalline forms $\alpha$, $\gamma$, and $\delta$. Although X-ray diffraction patterns showed a totally amorphous system, the PDF method revealed structural memory of the crystalline $\gamma$ form, which is considered to have a "seeding effect" and could cause re-crystallisation.[18]

As there is little knowledge about the underlying chemical mechanisms which lead to stable behavior of extrudates, their composition is currently optimized on an empirical basis. The aim of the present study was to apply PDF as a novel tool to obtain insight into the structure of the amorphous extrudates, with a view of correlating the results to the dissolution behavior. Extrudates prepared with felodipine, a $Ca^{2+}$-antagonist, and EUDRAGIT® polymers (Fig. 1) were chosen to exemplify melt extrusion products. EUDRAGIT® E is a cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters, the average molecular weight is approximately 150,000 Da. EUDRAGIT® NE is based on ethyl acrylate and methyl methacrylate, the molecular weight is approximately 800,000 Da. Usual characterization methods such as dissolution, DSC, XRPD, IR-, Raman- and $^{13}C$ NMR-spectroscopy were carried out and compared with results from PDF.

## EXPERIMENTAL

### Materials

Felodipine was purchased from Zhejiang Yiyuan, China, EUDRAGIT® E PO and EUDRAGIT® NE 30 D from Evonik Röhm GmbH, Pharma Polymers (Darmstadt, Germany). All organic solvents were high liquid performance (HPLC) grade and all other chemicals were reagent grade.

### Methods

#### *Preparation of Extrudates*

EUDRAGIT® E was chosen as a carrier due to its good thermoplastic properties, such as a low glass

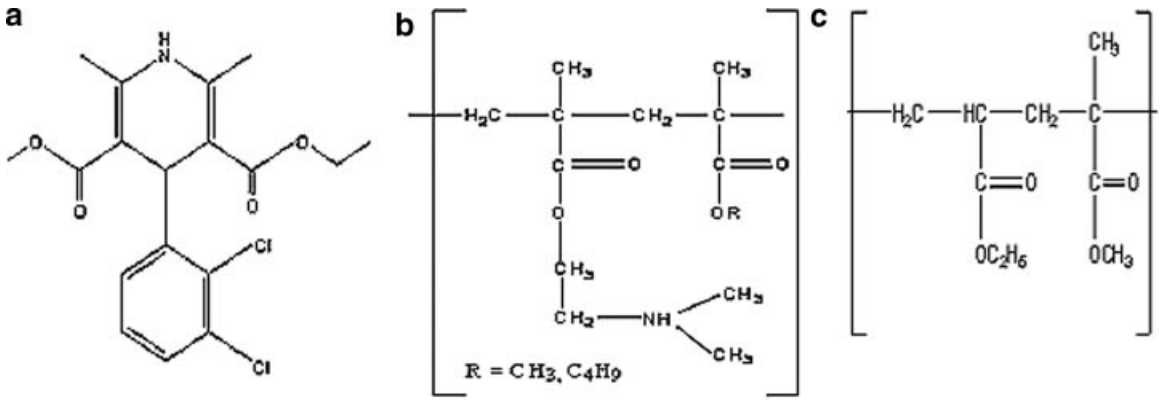


**Figure 1.** Structure of (a) felodipine (b) EUDRAGIT® E and (c) EUDRAGIT® NE (solid).

transition temperature (50°C) and thermal stability over the temperature range required for processing and because it dissolves rapidly in acidic media.

Felodipine, a dihydropyridine derivate administered in the treatment of hypertension, was chosen as the model drug, having a neutral character, a moderate melting point (145°C), thermal stability at processing temperature, low aqueous solubility (<1 mg/L at 37°C) and low dosage (10 mg).

Physical mixtures of EUDRAGIT® E and felodipine were prepared by mixing the substances in a double cone mixer (Erweka, Heusenstamm, Germany) for 15 minutes. Table 1 lists the composition of the extrudates. The first three extrudates contained EUDRAGIT® E and felodipine (extrudates 1–3). In subsequent experiments EUDRAGIT® NE was added to EUDRAGIT® E and felodipine (extrudates 4–7). All extrudates were manufactured with a corotating twin screw extruder (Leistritz MICRO 18 GL 40 D Pharma, Leistritz, Germany). The screw rate was set at 200 rpm; the temperature settings of the heating zones are listed in Table 2.

EUDRAGIT® E/felodipine mixtures were fed into the extruder at a constant feed rate of 0.7 kg/h. For extrudates 4–7, EUDRAGIT® NE 30D was fed into the extruder with a hose pump, one cylinder down-line from the feeding zone of the EUDRAGIT® E/felodipine mixture.

The resulting melts were homogenized, mixed and pushed through a single die (0.5 mm) under pressure. The strand was collected on a conveyer belt cooled with air and then granulated. The granules were cooled with liquid nitrogen and milled in a Retsch ultracentrifugal mill with a 250 μm sieve. The resulting powder was sieved (<250 μm) to exclude coarse particles.

### *Dissolution Studies*

Dissolution of the extrudates, the physical mixtures and the crystalline drug was characterized using a calibrated dissolution tester according to USP method 2. The paddle speed was set at 100 rpm and samples equivalent to 10 mg of felodipine were added to 500 mL simulated gastric fluid sine pepsin pH 1.2 heated to $37 \pm 0.5$°C.

Five milliliter samples were withdrawn at predetermined times (5, 10, 15, 30, 60, 90, 120 min) and filtered through 0.45 μm PTFE filter (Rezist® 30/0.45 membrane filter, Schleicher&Schüll, Dassel, Germany). After discarding the first

**Table 1.** Compositions of Extrudates Containing Felodipine, EUDRAGIT® E and EUDRAGIT® NE

| | Formulation | | | | | | |
|---|---|---|---|---|---|---|---|
| Substance | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Felodipine (%) | 50 | 30 | 10 | 10 | 10 | 10 | 10 |
| EUDRAGIT® E PO (%) | 50 | 70 | 90 | 87.5 | 85 | 82.5 | 80 |
| EUDRAGIT® NE (solid) (%) | — | — | — | 2.5 | 5 | 7.5 | 10 |

 DOI 10.1002/jps

**Table 2.** Temperature Settings for the Extrusion Process

| Heating Zones | Feeding | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Die |
|---|---|---|---|---|---|---|---|---|---|
| Temperature (°C) | 0 | 70 | 100 | 140 | 160 | 150 | 140 | 140 | 140 |

2 mL the remaining sample was immediately diluted with methanol. The removed volume was replaced with fresh media, held in a separate vessel at 37°C.

The concentration of the dissolved active was analyzed with HPLC. All dissolution tests were conducted in triplicate.

### *HPLC Analysis*

The HPLC system consisted of a Merck Hitachi HPLC pump L-7110, a Bischoff Autosampler 728 and a Bischoff Lambda 1000 UV-VIS-Detector. Felodipine was analyzed at 362 nm by using a LiChrospher 100, RP-18, $125 \times 4$ (5 μm) column (Merck KGaA, Germany). The mobile phase consisted of acetonitril, phosphate buffer pH 3.0 and methanol (40/40/20 v%/v%/v%) and the flow rate was set at 1 mL/min. The usual retention time under these conditions was 9 min and peak areas were calculated using Borwin integration software.

Standard solutions were freshly prepared for each experiment in methanol and linearity was verified over the concentration range 0.03 to 30 mg/L.

### *DSC*

DSC trials were performed for the drug, physical mixtures and extrudates using a Pyris 1 calorimeter (Perkin Elmer, Waltham, USA). Samples were prepared in sealed aluminum pans with a pierced lid. The samples were heated at 10°C/min under nitrogen atmosphere in a temperature range between 0 and 150°C. The first heating profile was used to determine the melting point and the melting enthalpies of the samples. As the glass transition temperature is masked by a thermal relaxation, samples were rapidly cooled at a rate of 20°C/min to 0°C after the first heating and heated a second time at 10°C/min to remove thermal history and thus enable the determination of the glass transition temperature.

### *Standard X-Ray Powder Diffraction*

XRPD was used to assess the solid state of the extrudates. Samples were evaluated using an X'Pert Pro X-ray diffraction system consisting of a Cu Kα radiation source and an X'Celerator detector. Angle calibration is carried out using the control of the peak position of the silicium standard. Each diffractogram was recorded between $4^\circ < 2\theta < 74^\circ$.

### *FT-IR-Spectroscopy*

IR spectra of the pure drug, pure polymers and of the extrudates were obtained with a Nicolet 5700 FT-IR (ThermoFisher Scientific, Waltham, USA), using KBr disks. The transmission was recorded in the spectral region of 450–4000 $cm^{-1}$.

### *Raman-Spectroscopy*

Raman-spectroscopy was performed by using a Jobin-Yvon/Horiba Raman spectrometer (LabRam), equipped with a 632 nm laser. Silicon was used to calibrate the wavelength. Spectra were collected at room temperature under the following conditions: 50× microscope objective, 1000 μm slit width and 7 s exposure time.

### *$^{13}$C-NMR Spectroscopy*

The $^{13}$C solid state NMR spectra were measured on a Varian Unity 400 equipped with a Chemagnetics T3 Narrow Bore MAS Probe. Rotation of the powdered sample (ca. 50 mg) at the magic angle was performed at a frequency of approximately 9–10 kHz using $ZrO_2$ pencil rotors with a 4 mm diameter (52 μL). The standard cross-polarization pulse sequence was used. The spectra were referenced to external Trimethylsilylpropionicacid sodium salt. Spectra from the pure polymer EUDRAGIT® E100 and the compounds with the drug were obtained in the solid state. EUDRAGIT® NE was measured in solution. The peak at 39.6 ppm in the EUDRAGIT® NE spectra corresponds to the DMSO-d6.

### *PDF*

PDFs were obtained from X-ray powder diffractograms collected from $4^\circ < 2\theta < 120^\circ$ on an STOE Stadi P diffractometer (flat plate transmission

geometry) using Ge(1 1 1) monochromatized Cu $K\alpha_1$ radiation and a linear position sensitive detector. The background corrected diffractograms were normalized[16] and Fourier transformed to the PDF $G(r)$ using the software PDFgetX2.[19]

## RESULTS AND DISCUSSION

### Dissolution Studies

Figure 2a compares the dissolution rate of extrudates containing different ratios of felodipine with the unprocessed crystalline drug and a physical mixture containing 90% EUDRAGIT® E and 10% felodipine. With increasing percentage of polymer the extent of dissolution is improved, leading to a 360-fold dissolution enhancement of the drug in case for the extrudate containing 10% felodipine. A similar effect of EUDRAGIT® E on dissolution has been reported for a coevaporate containing EUDRAGIT® E and benidipine.[20]

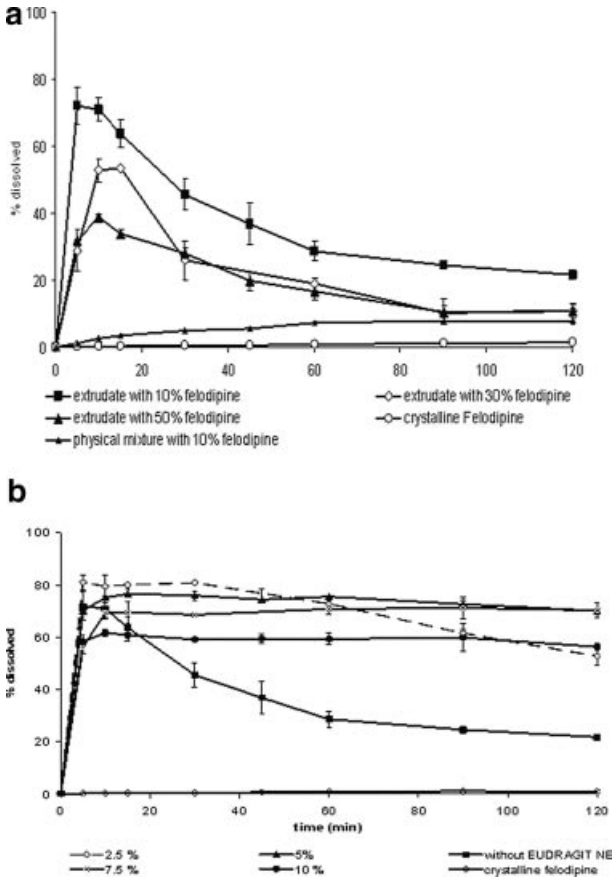


**Figure 2.** Dissolution profile of extrudates in SGFsp pH 1.2 ($n = 3$, ±SD), (a) Containing felodipine and EUDRAGIT® E, compared with the crystalline drug and the physical mixture, (b) Containing different percentages of EUDRAGIT® NE compared with the crystalline drug and the extrudate containing EUDRAGIT® E and felodipine 90:10.

EUDRAGIT® E dissolves rapidly and forms a polymer-rich phase in which the drug molecules can dissolve. Due to the rapid dissolution, a highly supersaturated solution of the drug is generated, resulting in fast recrystallization of the drug and a subsequent decline in concentration. Itraconazol[21] and 9,3-diacetylmidecamycin[22] are other examples of drugs which tend to recrystallize from a supersaturated solution.

The increase in dissolution is not caused by the simple mixture of the polymer and the drug. Compared to the pure crystalline drug, the extent of dissolution is slightly improved in case of the physical mixtures, induced by the wetting properties of the polymer, but far below the extent achieved with the glassy extrudate.

Various hydrophilic polymers are known to inhibit the precipitation of drugs. For example, water-soluble polymers like PVP, HPMC, and HPC had an inhibitory effect on the precipitation of RS-8359 from a supersaturated solution.[23] In this study, the use of a water-insoluble polymer to inhibit recrystallization was evaluated. EUDRAGIT® NE was added during extrusion to stabilize the drug in the supersaturated solution (Fig. 2b). 2.5% of EUDRAGIT® NE is not sufficient to inhibit the precipitation completely, but the recrystallization rate is retarded. 5% EUDRAGIT® NE appears to be the optimum percentage, as the initial dissolution rate is still as high as for the formulation containing only EUDRAGIT® E and felodipine, but precipitation is circumvented. At 7.5 and 10% there is a decrease in the extent of felodipine dissolution. At higher levels of EUDRAGIT® NE, the volume of the EUDRAGIT® E-rich phase around the molecules is reduced and as EUDRAGIT® NE is insoluble, it cannot contribute to the felodipine dissolution.

### DSC

The amorphous state is known to enhance the dissolution rate, as no lattice energy has to be overcome. For example, Hancock and Parks[24] reported a fivefold increase in solubility for indomethacin compared to the crystalline drug. A decline in concentration was observed after 10 min. Heating felodipine together with silicon dioxide led to a significant improvement of felodipine dissolution rate.[25]

DSC studies were therefore performed to analyze the physical state of the extrudates and their components.

DSC of crystalline felodipine shows a melting peak at 146°C in the first heating step with a heat of fusion of 80.65 J/g. After cooling the sample rapidly, the second heating exhibits a glass transition temperature at 35°C. EUDRAGIT® E is an amorphous polymer and exhibits a glass transition temperature of 50°C.

With increasing drug load, the physical mixtures of the crystalline drug and EUDRAGIT® E show a slight decrease in the melting point in the first heating run and a decrease in glass transition temperature in the second heating run, indicating a plastizing effect of the drug on the polymer. As only one glass transition temperature is measured, complete miscibility of the two components can be assumed (Tab. 3).

The values of crystallinity were calculated using the heat of fusion of the pure felodipine according to its amount present in the physical mixture and the measured heat of fusion of felodipine in the physical mixtures.

In the extrudate the drug is in an amorphous state as no melting point is observed in the first or the second run at all ratios (Tab. 4). Furthermore, solute felodipine molecules serve as a plasticizer, decreasing the glass transition temperature according to the concentration of the drug. The fact that only one glass transition temperature is observed confirms the complete miscibility of the drug and the polymer[26] and indicates that a glassy solution has been formed.

Extrudates containing EUDRAGIT® NE also exhibited only one glass transition temperature and no melting peak, indicating that, here too, amorphous felodipine is present as a solid solution (Tab. 4).

From the DSC results it appears that the dissolution rate enhancement is caused by conversion of felodipine to the amorphous state, which offers a low thermodynamic barrier to solution and the formation of a glassy solution, where the drug is molecularly dispersed in the carrier. The wetting properties of the polymer may also contribute to the enhanced dissolution.

**Table 3.** DSC Results for Physical Mixtures Containing EUDRAGIT® E and Felodipine

| $w$ (%/%) | $T_{onset}$ (°C) | Heat of Fusion (J/g) | Crystallinity (%) | $T_g$ (°C) |
|---|---|---|---|---|
| 90/10 | 139 | 6.1 | 75.8 | 39 |
| 70/30 | 134 | 26 | 100 | 36 |
| 50/50 | 136 | 39 | 96.3 | 35 |

**Table 4.** DSC Results for Extrudates Containing Felodipine, EUDRAGIT® E and EUDRAGIT® NE

| Felodipine | EUDRAGIT® E | EUDRAGIT® NE (Solids) | $T_g$ (°C) |
|---|---|---|---|
| 10 | 90 | | 33 |
| 10 | 70 | | 32 |
| 10 | 30 | | 30 |
| 10 | 87.5 | 2.5 | 35 |
| 10 | 85 | 5 | 38 |
| 10 | 82.5 | 7.5 | 40 |
| 10 | 80 | 10 | 41 |

## X-Ray Powder Diffraction

XRPD was used to confirm the DSC results. The X-ray diffractograms of the extrudates containing only EUDRAGIT® E were compared with the pure drug.

No peaks were apparent in the extrudates, indicating an amorphous, probably dissolved, state of the drug (Fig. 3).

X-ray diffraction patterns of ternary extrudates were recorded in the course of the PDF study and will be discussed there.

## IR-Spectroscopy and Raman-Spectroscopy

Felodipine is able to act as a hydrogen bonding donor[27,28] and therefore can react with a hydrogen bonding acceptor group of a second molecule. This has been observed for various polymers, for

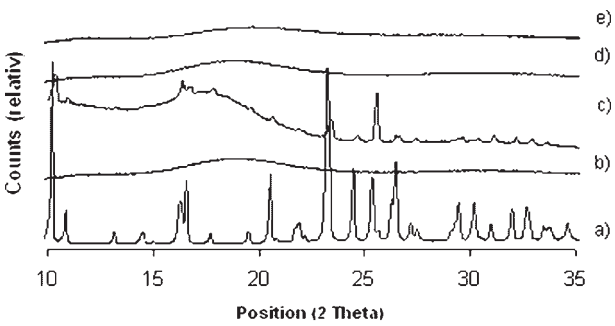


**Figure 3.** X-ray pattern of (a) crystalline felodipine, (b) extrudates with EUDRAGIT® E:felodipine 90:10, (c) Physical mixture with EUDRAGIT® E and felodipine 90:10, extrudates with EUDRAGIT® E:felodipine (d) 70:30, and (e) 50:50.

example, HPMC, HPMCAS and PVP[29] and PEG[30], all of which decrease the nucleation rate of felodipine by forming hydrogen bonds. With quantum mechanical modeling of drug–polymer interactions it was revealed that hydrogen bonds with the carbonyl groups of PVP are stronger than for PEG[30] This finding can be transferred to the liquid state as shown by Kim et al.,[31] who prepared solid dispersions with PVP and HPMC by a solvent wetting method. The dissolution rate of amorphous felodipine was increased and almost no recrystallization from the supersaturated solution was observed.

It was proposed that hydrogen bonds or other interactions between EUDRAGIT® NE and felodipine inhibit the precipitation of the drug after dissolution; therefore IR- and Raman-spectroscopy were performed. Ambiguities interpreting the IR spectra arose from the similarity of the functional groups in the two polymers. Both polymers show strong CH-X vibrations at around 2950, 1450, and 1385 $cm^{-1}$, the characteristic bands of the ester groups at 1150–1190, 1240 and 1270 $cm^{-1}$ and the C = 0 ester vibration at 1730 $cm^{-1}$. EUDRAGIT® E additionally shows absorptions at 2770 and 2820 $cm^{-1}$ for the dimethylamino group. Felodipine shows a peak at around 3370 $cm^{-1}$ corresponding to the amino group in the dihydropyridine ring, an absorption at 1700 $cm^{-1}$ for the ester groups and a C=C vibration at 1646 $cm^{-1}$ for the dihydropyridine ring. A shift of the NH-group, caused by H-bonds, could not be observed.

Raman spectroscopy results are shown in Figure 4.1. Felodipine (Fig. 4.1a) has a characteristic peak at 3375 $cm^{-1}$ for the NH stretching

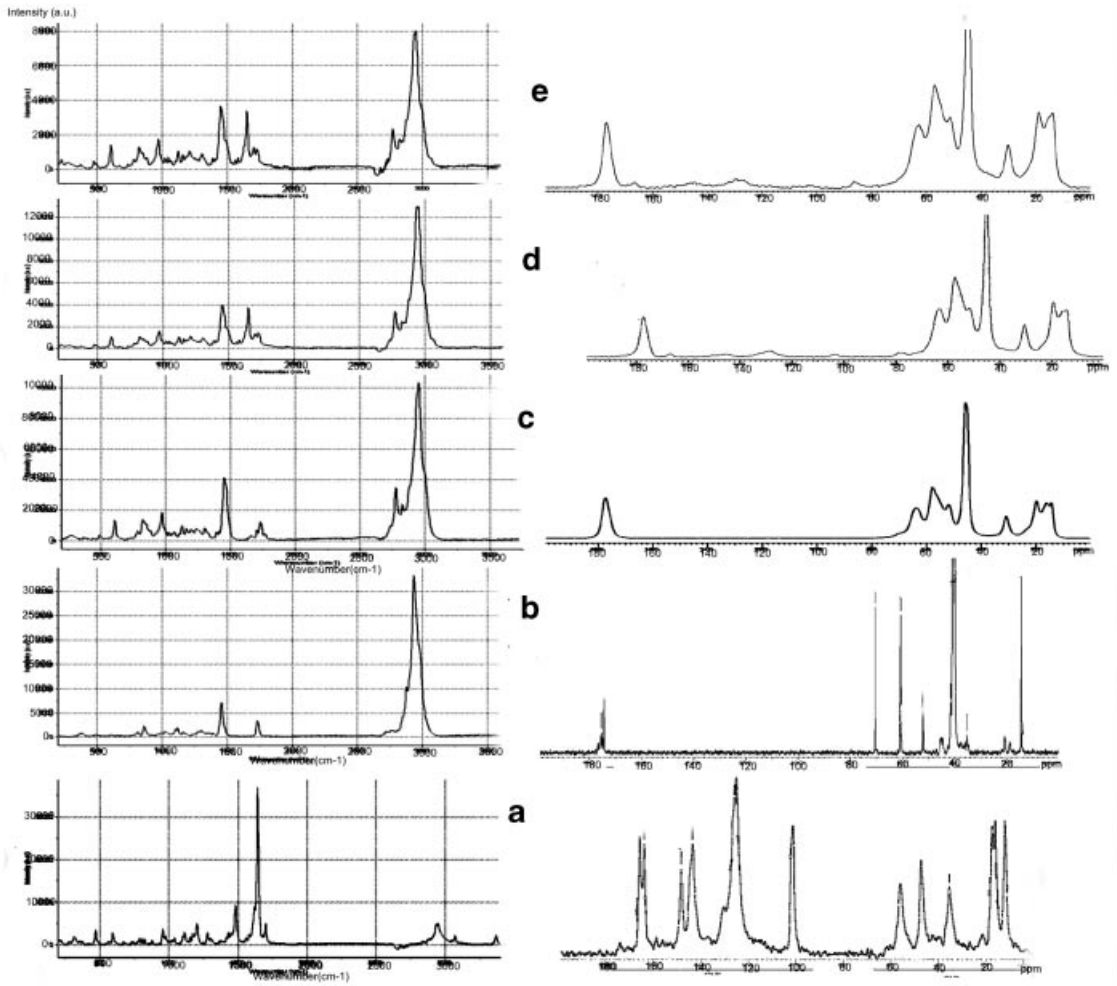


**Figure 4.** (4.1) Raman- and (4.2) $^{13}$C-NMR spectra of (a) Felodipine, (b) EUDRAGIT® NE, (c) EUDRAGIT® E, (d) extrudate with 10% felodipine, 85% EUDRAGIT® E and 5% EUDRAGIT® NE, and (e) extrudate containing 10% felodipine and 90% EUDRAGIT® E.

vibration and a characteristic peak at 1639 $cm^{-1}$ attributed to the free carbonyl stretching mode (Fig. 4.1a). EUDRAGIT® E and EUDRAGIT® NE show strong C-H vibrations at around 2865 and 2954 $cm^{-1}$, respectively, and peaks can be assigned to the C=O vibrations of the ester groups at 1732 and 1742 $cm^{-1}$, respectively (Fig. 4.1b and c).

Comparison of extrudates (Fig. 4.1d and e) with and without EUDRAGIT® NE showed no differences in the spectra of the polymers, most likely due to the low amount of EUDRAGIT® NE in the combination extrudates. A shift of the NH group of felodipine (at 3375 $cm^{-1}$) to higher wavelengths would indicate interactions like hydrogen bonds. The absence of this characteristic peak is probably also due to the low concentration of the substance. In summary, neither technique revealed any specific evidence for interactions nor could they explain the differences in the dissolution behavior of the extrudates.

### $^{13}$C-NMR Spectroscopy

Figure 4.2 shows spectra of Felodipine (a), EUDRAGIT® NE, EUDRAGIT® E and the extrudates. The pure felodipine (Fig. 4.2b) is present in crystalline form, which hinders the rotation of the phenyl ring. Therefore the two ester groups are spectroscopical distinguishable (peaks at 163 and 165 ppm). In the extrudate (Fig. 4.2b) only one peak is observed, at 166 ppm. This can be explained by the amorphous state of the drug or a free rotation of the ring. All signals of the pure drug are broadened in the extrudates due to the change of the chemical environment in the solution.

The chemical shifts of EUDRAGIT® E in the extrudates deviate only marginally from the shifts of the pure polymer. No evidence for intermolecular interactions could be detected.

### PDF Analysis

As little information about interactions between the components of the formulation could be obtained via standard spectroscopic techniques, PDF analysis was applied. Figure 5 compares the diffractograms and PDFs of pure EUDRAGIT® E, crystalline felodipine and the extrusion product of EUDRAGIT® E with 10% felodipine. From the PDF data it can be clearly seen that the drug in

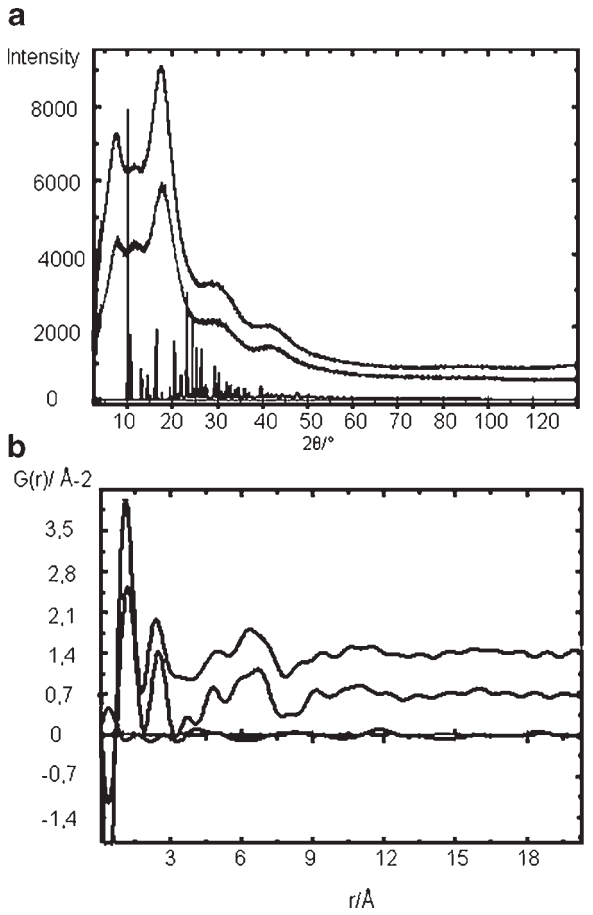


**Figure 5.** (a) Powder diffractograms of EUDRAGIT® E (top), felodipine (lower) and 10% felodipine extruded with EUDRAGIT® E (middle). (b) The corresponding PDFs: EUDRAGIT® E (top, offset + 1.2 $Å^{-2}$), felodipine (lower) and 10% felodipine extrudated with EUDRAGIT® E (middle, offset + 0.6 $Å^{-2}$); the PDF of felodipine (lower) was scaled to 0.1. The differences between loaded and unloaded polymer are not significant, the correlations in the amorphous material cease to exist around $r > 15$ Å.

all samples is entirely dispersed after extrusion. Crystalline peaks are not observed in the diffractogram, nor can any additivity of the single PDFs be seen. The same observation holds for EUDRAGIT® NE (data not shown). Figure 6 compares diffractograms and PDFs of the polymers EUDRAGIT® E and EUDRAGIT® NE. The two polymers differ most distinctly in the region 4.5 Å $< r <$ 12.0 Å, corresponding to the different sequences of their building blocks. Figure 7 shows how the medium range structure of the extrudate (EUDRAGIT® E:NE:felodipine = 85:5:10) differs from the pure polymers. The PDFs are not

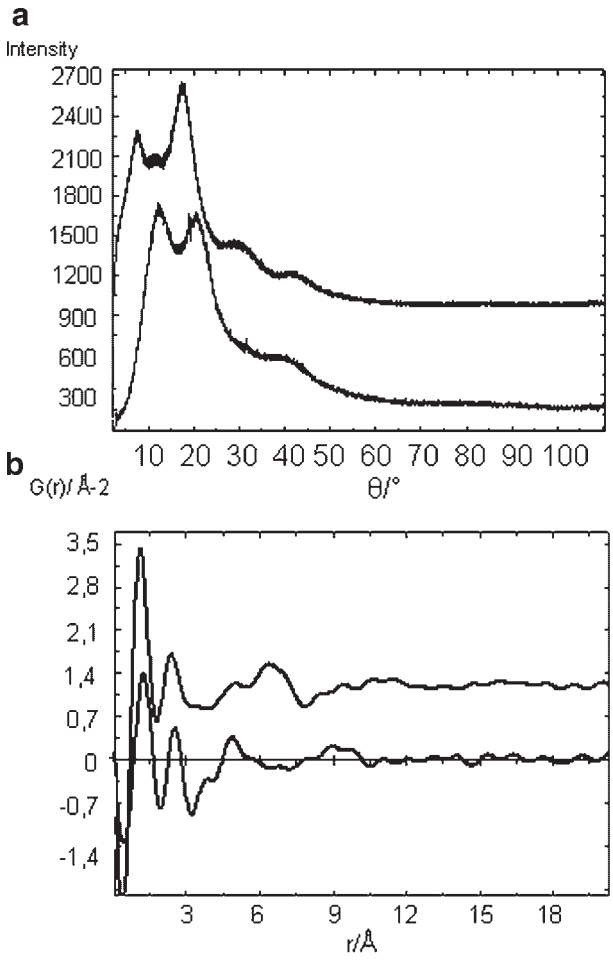


**Figure 6.** (a) Powder diffractogram of EUDRAGIT® E (top) and EUDRAGIT® NE (lower). (b) The corresponding PDFs of EUDRAGIT® E (top, offset + 1.2 $Å^{-2}$) and EUDRAGIT® NE (lower); the polymers visibly differ in the range 4 Å < $r$ < 12 Å.

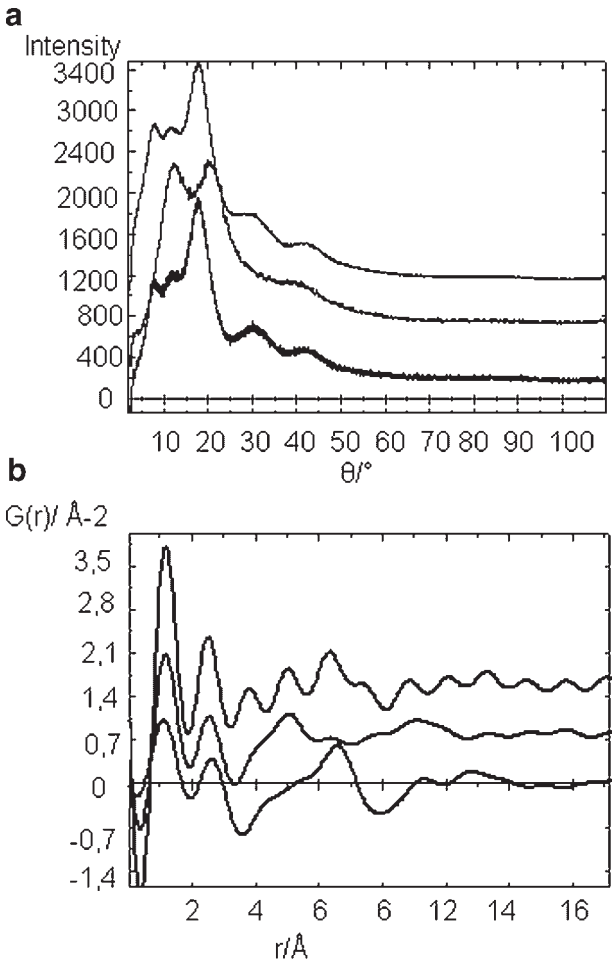


**Figure 7.** (a) Powder diffractograms of EUDRAGIT® E (top), EUDRAGIT® NE (middle) and the extrusion product of EUDRAGIT® E:EUDRAGIT® NE:felodipine 85:5:10 (lower). (b) The corresponding PDFs of EUDRAGIT® E (top, offset + 1.6 $Å^{-2}$), EUDRAGIT® NE (middle, offset + 0.8 $Å^{-2}$) and the extrusion product of EUDRAGIT® E:EUDRAGIT® NE:felodipine 85:5:10 (lower); the structure of EUDRAGIT® E is broken up at $r \approx 5$ Å and correlations in the structure are shifted to $r \approx 6$ Å.

additive; the medium range is drastically changed. There is a shift in maxima of atomic pairs from 5.0 to 6.5 Å. We interpret this change in terms of a different secondary arrangement of polymer blocks; the structure of EUDRAGIT® E is disturbed by the addition of a small amount of EUDRAGIT® NE. The dispersion of the felodipine molecule inside this arrangement, and—most important—the retention in this "mask" during dissolution in gastric simulating media, may lead to the more stable dissolution profile observed.

It will be of interest to further investigate whether this behavior is observed with other drugs extruded using EUDRAGIT® and a systematic study should be performed including other polymers.

## CONCLUSION

Dissolution rate improvement was obtained by preparing solid solutions of felodipine and EUDRAGIT® polymers via melt extrusion. Although an acid-soluble polymer alone greatly improves the dissolution, the addition of minor amounts of a water-insoluble polymer is necessary to stabilize the supersaturation. In contrast to standard methods of analysis (DSC, XRD, IR-, Raman-, $^{13}$C-NMR-spectroscopy), PDF analysis was able to describe order in the amorphous state,

and detect differences in this characteristic between the various polymer extrudate systems. PDF thus shows promise with respect to understanding the dissolution behavior of drugs from polymer extrusion products.

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