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Characterization and stability of solid dispersions based on PEG/polymer blends

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ABSTRACT

Solid dispersions were prepared by a melting method from the water-insoluble model drugs carbamazepine and nifedipine and polyethylene glycol 1500 (PEG 1500) or 1:1 mixtures of PEG 1500 and the polymers polyvinylpyrrolidone (PVP 30, PVP 12), polyvinylpyrrolidone-co-vinylacetate (PVPVA) and Eudragit EPO (Eudragit) in order to combine advantages of the different carrier polymers (recrystallization inhibition, processability and stability). The solid dispersions were characterized by dissolution, powder X-ray diffractometry and microscopy directly after preparation and after storage for 3 and 6 months at 25 °C/0% relative humidity (RH) or 3 months at 40 °C/75% RH. More than 80% drugs were released from all solid dispersions within 20 min. The dissolution rate of carbamazepine decreased in the order of PEG 1500 > PEG 1500/Eudragit > PEG 1500/PVP 30 > PEG 1500/PVPVA > PEG 1500/PVP 12. The dissolution rank order was not directly correlated to the amorphous/crystalline state of the drugs, but rather to the properties of the PEG 1500/polymer compositions. Nifedipine was released in the order of PEG 1500 > PEG 1500/PVPVA > PEG 1500/PVP 30 > PEG 1500/PVP 12 > PEG 1500/Eudragit. Amorphous nifedipine was present in all PEG 1500/polymer dispersions except in pure PEG 1500 solid dispersion. The significant increase in dissolution rate of PEG 1500 solid dispersions was due to the reduced crystallinity of the drug and the excellent solubilisation properties of PEG 1500. After 6 months storage at 25 °C/0% RH, the solid dispersions released both drugs in the order PEG 1500/PVPVA > PEG 1500/PVP 30 > PEG 1500/PVP 12 > PEG 1500/Eudragit > PEG 1500. The stabilized amorphous state of the drug resulted in stable dissolution profiles of PEG 1500/PVPVA, PEG 1500/PVP 30 and PEG 1500/PVP 12 when compared to the PEG 1500 solid dispersions, which contained a higher amount of crystalline drug. The solid dispersions with PEG 1500/PVPVA or PEG 1500/PVP stored for 3 months at 40 °C/75% RH showed phase separation due to the hygroscopic properties of the polymers. The influence of 10% (w/w) of the solubilisers polyoxyl 40 hydrogenated castor oil (Cremophor), macrogol-15-hydroxystearate (Solutol) and fatty alcohol alkoxylate (Pluronic) on the dissolution rate and the physical state of the drug was significant.

1. Introduction

The concept of solid dispersions dates back to 1961 when Sekiguchi & Obi found that the administration of a fused mixture of the poorly water-soluble drug sulphathiazole and the water-soluble carrier urea produced an enhanced absorption of the drug in rabbits. Subsequently, hundreds of papers have been published detailing the physico-chemical properties, phase equilibrium and pharmacological activity of solid dispersion-based drug-carrier systems (Ford and Timmins, 1989). However, only few drug products based on solid dispersions have reached the market, mainly because of physico-chemical instability and scale-up problems (Serajuddin, 1999; Craig, 2002).

Solid dispersions are generally prepared by either a solvent method, whereby the drug and carrier are dissolved in a mutual solvent followed by solvent removal, or by a melting method, whereby drug-carrier mixtures are prepared by co-melting/cooling. The disadvantage of the solvent method is the use of organic solvents with issues of toxicity, safety hazards and solvent residuals and also the possible precipitation of the drug into various polymorphic forms, which have different solubilities and bioavailabilities. Therefore, melting is often the method of choice for the preparation of solid dispersions despite the potential problem of heat-induced degradation of drugs and carriers.

PEGs are widely used as vehicles for solid dispersions because of their low melting point, rapid solidification rate, capability of forming solid drug solutions, low toxicity and low costs (Betageri and Makarla, 1995; Chiou and Riegelmann, 1969; Craig, 1990; Doshi et al., 1997). However, at higher drug concentrations, the drug is often present in the crystalline form within the PEG dispersion or it recrystallizes over time, resulting in unstable formulations

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with lower dissolution rates (Franko et al., 2001; Markovich et al., 1998).

The ability to stabilize the amorphous state of drugs due to inhibition of drug recrystallization as well as a rapid solidification rate and low toxicity favors the polymers polyvinylpyrrolidone-co-vinylacetate (PVPVA) and polyvinylpyrrolidone (PVP) for the preparation of solid dispersions (Friedrich, 2004; Shamblin and Zografi, 1998; Yoshioka et al., 1995). PVPs are amorphous polymers with glass transition temperatures between 110 and 180 °C. However, the relatively high glass and melting transitions limit the applicability of these polymers for the preparation of solid dispersion by the melting method (Friedrich, 2004).

The aim of this study was to use blends of PEG 1500 and PVPs or PVPVA for the preparation of solid dispersions by the melting method. Co-melting PEG 1500 with PVP or PVPVA could combine the positive and offset the negative properties of PEG 1500 (low melting temperature, solubiliser) and of the polymers PVP 30, PVP 12 and PVPVA (high melting temperature, recrystallization inhibitor, solubiliser) with regard to processability, drug release and stability. In addition, the influence of the solubilisers polyoxyl 40 hydrogenated castor oil (Cremophor), macrogol-15-hydroxystearate (Solutol) and fatty alcohol alkoxylate (Pluronic) on the dissolution rate and physical stability of nifedipine in PEG 1500/PVP 30 solid dispersion was investigated.

2. Materials and methods

2.1. Materials

Micronized nifedipine (Tm = 173 °C) and carbamazepine (Tm = 190 °C) (Sigma–Aldrich Laborchemikalien GmbH, Seelze, Germany), polyvinylpyrrolidone (PVP 30, PVP 12, Kollidon® 30, Kollidon® 12), polyvinylpyrrolidone-co-vinylacetate (PVPVA, Kollidon® VA 64), polyethylene glycol (PEG 1500, Lutrol® E 1500) (BASF AG, Ludwigshafen, Germany), Eudragit EPO (Eudragit) (Röhm GmbH, Darmstadt, Germany), polyoxyl 40 hydrogenated castor oil (Cremophor, Cremophor® RH), macrogol-15-hydroxystearate (Solutol, Solutol® HS) (BASF AG, Ludwigshafen, Germany), copolymer of ethylene oxide and propylene oxide 237 (Pluronic, Pluronic® F87NF) (BASF AG, Mount Olive, NJ, USA).

2.2. Preparation of solid dispersions

Solid dispersions were prepared by melting 3.75 g PEG 1500 at 140 ± 2 °C for 5 min in an aluminum pan on a heating plate (RCT basic, IKA Labortechnik, Staufen, Germany) under stirring with a magnetic stirrer, followed by the addition of 1.25 g drug powder (25%, w/w based on the mass of the solid dispersion) and stirring for an additional 5 min. The temperature on the heating plate was controlled by a contact thermometer (Testoderm GmbH&Co., Lenzkirch, Germany). The melt was then cooled in an ice bath for 10 min. Solid dispersions containing drug, PEG 1500 and polymer were prepared by melting 1.88 g (37.5%, w/w) PEG 1500 for 5 min, adding 1.88 g (37.5%, w/w) polymer and melting both materials at 140 ± 2 °C for 5 min under stirring. Finally, 1.25 g (25%, w/w) drug was added and the melt was stirred again for 5 min and cooled down in an ice bath for 10 min. Solid dispersions containing drug, PEG 1500, polymer and solubiliser consisted of 32.5% (w/w) PEG 1500, 32.5% (w/w) PVP 30, 10% (w/w) solubiliser and 25% (w/w) nifedipine. The solubiliser and then the drug were added to the molten PEG 1500 and polymer, followed by the same procedure as above.

After 24 h storage in a desiccator, the solid dispersions were pulverized in a Teflon ball mill under nitrogen cooling at 70 rpm for 10 min (mixer mill MM 2000, Retsch, Hemer, Germany). After sieving and 24 h drying in a desiccator, the particle size fraction smaller than 100 μm was used for dissolution studies, and the particles size fraction 100–250 μm was used for all other studies. All experiments with nifedipine were carried out using dark glasses and under subdued light to prevent light-induced degradation of the drug.

2.3. Storage conditions

The solid dispersions were stored in a desiccator at 25 ± 2 °C over H_2SO_4 and in a stability oven (Weiss Umwelttechnik GmbH, Reiskirchen-Lindenstruth, Germany) at 40 °C and 75% RH. The solid dispersions were characterized by dissolution studies, X-ray diffractometry and microscopy directly after preparation, and after 3 and 6 months.

2.4. Solubility and dissolution studies

An excess amount of drug was placed into a vial with 5 ml water. The samples were shaken for at least 5 days at 25 ± 2 °C. 2 ml samples were taken from the saturated solutions, and filtered through a 0.5 μm filter (Sartorius AG, Göttingen, Germany). The

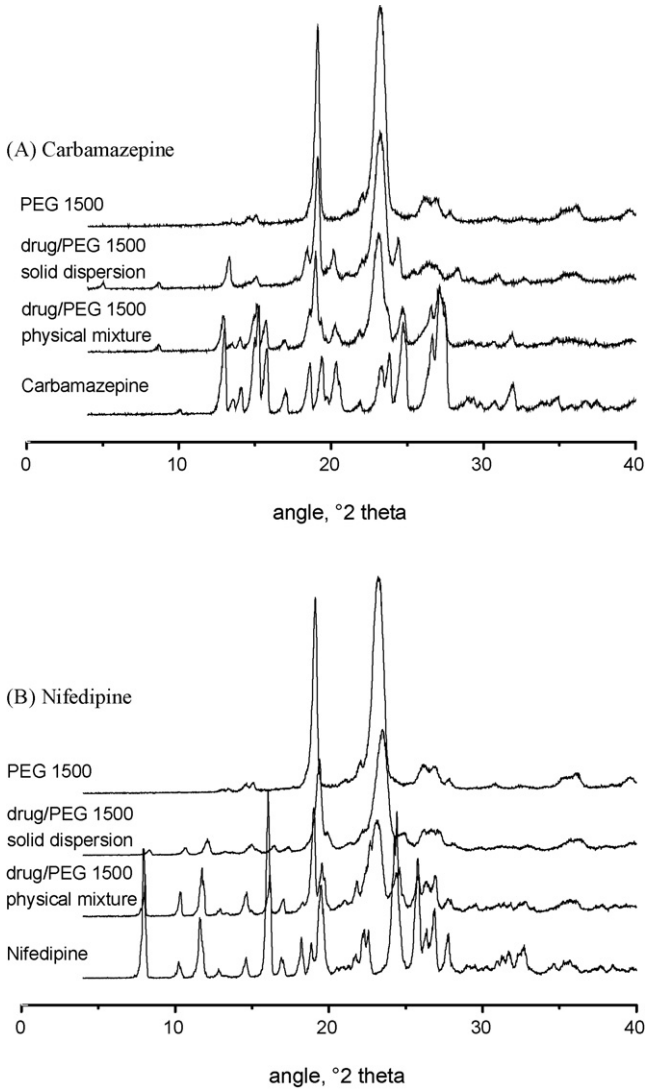


Fig. 1. X-ray patterns of drug, PEG 1500, drug/PEG 1500 physical mixtures and drug/PEG 1500 solid dispersions (drug: PEG; 1:3, w/w): (A) carbamazepine, (B) nifedipine.

drug concentration was detected UV-spectrophotometrically after appropriate dilution with demineralized water and equated to the drug solubility.

Dissolution studies were performed with solid dispersions containing 5 mg carbamazepine or 2.5 mg nifedipine in 900 ml demineralized water (pH 6.5 ± 0.3) at 37 °C and 100 rpm with the USP XXV rotating paddle method (n = 3). 2 ml samples were withdrawn after 10, 20, 30, 40, 50 and 60 min and filtered through a 5 μm filter (Sartorius AG, Göttingen, Germany). The drug concentrations were detected UV-spectrophotometrically at λ = 238 nm for nifedipine and λ = 286 nm for carbamazepine (UV 2101 PC, Shimadzu Scientific Instruments Inc., Columbia, MD, USA). Interference of the carriers was negligible. All experiments with nifedipine were carried out using dark glasses and under subdued light to prevent light-induced degradation of the drug.

2.5. Powder X-ray diffractometry

X-ray diffraction measurements of the solid dispersions were performed on a Philips PW 1830 X-ray generator with a copper anode (Cu Kα radiation, λ = 0.15418 nm, 40 kV), fixed with a Philips PW 1710 diffraction control unit (Philips Industrial & Electro-acoustic Systems Divisions, Almelo, The Netherlands). The radiation scattered in the crystalline regions of the samples was measured with a vertical goniometer (Philips PW 1820, Philips Industrial & Electro-acoustic Systems Division, Almelo, The Netherlands). Patterns were obtained using a step width of 0.02 °C with a detector resolution in 2θ between 4° and 40° at ambient temperature.

2.6. Microscopy

Solid dispersions were observed under an optical microscope (Axiotrop, Carl Zeiss Jena GmbH, Jena, Germany) connected to a digital camera. The pictures were displayed from the Easy Measure Software (version 1.0.15; INTEQ Informationstechnik GmbH, Berlin, Germany).

2.7. Moisture uptake

The moisture uptake of polymers was determined gravimetrically. 100–200 mg of the polymer powders were placed in chambers with controlled humidity at 25 ± 2 °C and weighed at different time points (Mettler AT 250, Toledo, Giessen, Germany). The chambers were equilibrated with saturated salt solutions of CH_3COOK to 22% RH, with K_2CO_3 to 44% RH, with NaCl to 74% RH, and $ZnSO_4$ to 85% RH at room temperature. The data are shown for the measurement at day 7, on which the sample weight was constant.

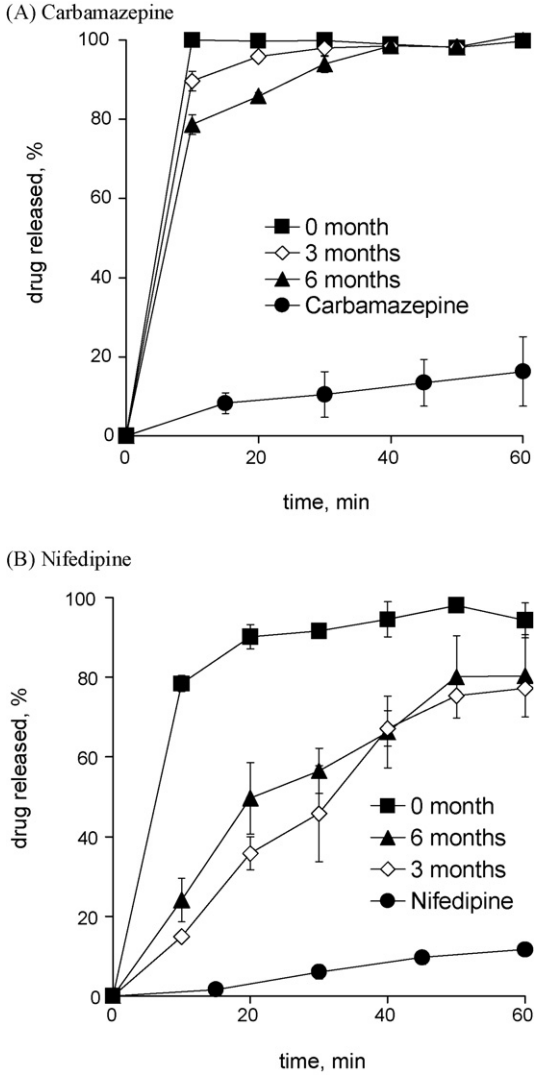


Fig. 2. Drug release from drug/PEG 1500 solid dispersions after preparation and storage for 3 and 6 months at 25 °C/0% RH: (A) carbamazepine, (B) nifedipine.

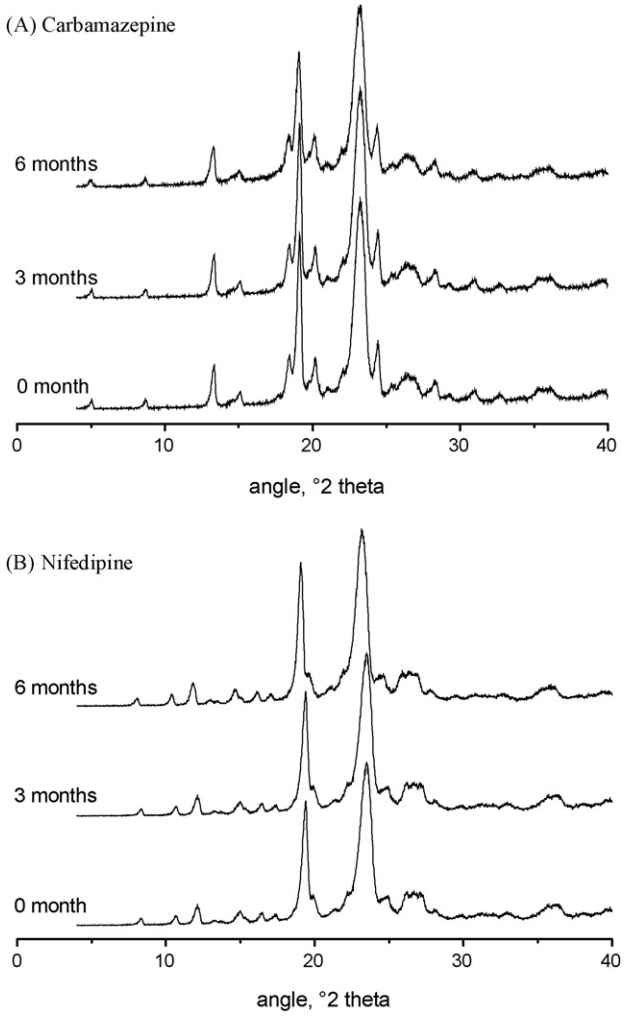


Fig. 3. X-ray patterns of drug/PEG 1500 solid dispersions after preparation (0 month) and storage for 3 and 6 months at 25 °C/0% RH: (A) carbamazepine, (B) nifedipine.

2.8. Differential scanning calorimetry (DSC)

4–8 mg of each polymer or solid dispersion was sealed in a 40 μl aluminum sample pan with three pin holes in the lid. The thermograms were recorded from 25 to 190 °C at 10 °C/min ($n = 2$) to determine the glass transition temperatures (Tgs) in a model 821e differential scanning calorimeter, (Mettler, Toledo, Giessen, Germany). The Tg values were derived from the computed extrapolated peak maximum using the Star® Software (Mettler, Toledo, Giessen, Germany).

3. Results and discussions

PEG 1500 solid dispersions were easy to produce by the melting method (Friedrich, 2004). 25% (w/w) of nifedipine or carbamazepine was dissolved in the PEG 1500 melt during preparation. Upon cooling, the drugs could either remain dissolved in the carrier (solid solution) or precipitate in amorphous or crystalline form (solid dispersion). Both drugs precipitated partially crystalline and amorphous after cooling/solidification of the melt, thus indicating the formation of solid dispersions (Fig. 1). A partial dissolution of the drug in the polymer could be feasible. Untreated carbamazepine showed peaks at approximately 10°, 13° and 15° 2θ, which were specific for form I (Lowes et al., 1987; McMahon et al., 1996; Otsuka et al., 2000) (Fig. 1A). PEG 1500 revealed two distinct peaks at 19° and 23° 2θ, characteristic of its crystalline nature (Fig. 1). The preparation of solid dispersion with PEG 1500 led to additional peaks between 5° and 8° 2θ, which were related to carbamazepine dihydrate (Krahn and Mielck, 1987; Kobayashi et al., 2000; McMahon et al., 1996) (Fig. 1A). As expected, the crystallinity of both drugs was higher in the physical mixtures. Polymorphic transitions of nifedipine were not observed in this study (Fig. 1B).

The carbamazepine/PEG 1500 and nifedipine/PEG 1500 solid dispersions showed higher dissolution rates compared to the micronized drugs. Within the first 10 min, approximately 100% of carbamazepine and 80% of nifedipine were dissolved (Fig. 2A and B). The amount of carbamazepine dissolved from the solid dispersions was approximately nine times and of nifedipine approximately eight times higher when compared to the pure drug. During the first minutes, the dissolution process was characterized by a high concentration of PEG 1500 around the drug particles. This affected the diffusion layer that surrounded the drug particles and thus improved the micro-environmental solubility, resulting in fast drug dissolution.

High drug-dosed PEG 1500 solid dispersions often gave unstable formulations, resulting in products with lower dissolution rates (Badwan et al., 1991; Betageri and Makarla, 1995; Franko et al., 2001; Markovich et al., 1998). The effect of aging on the dissolution rate of carbamazepine and nifedipine solid dispersions was also visible in this study. The drug release decreased

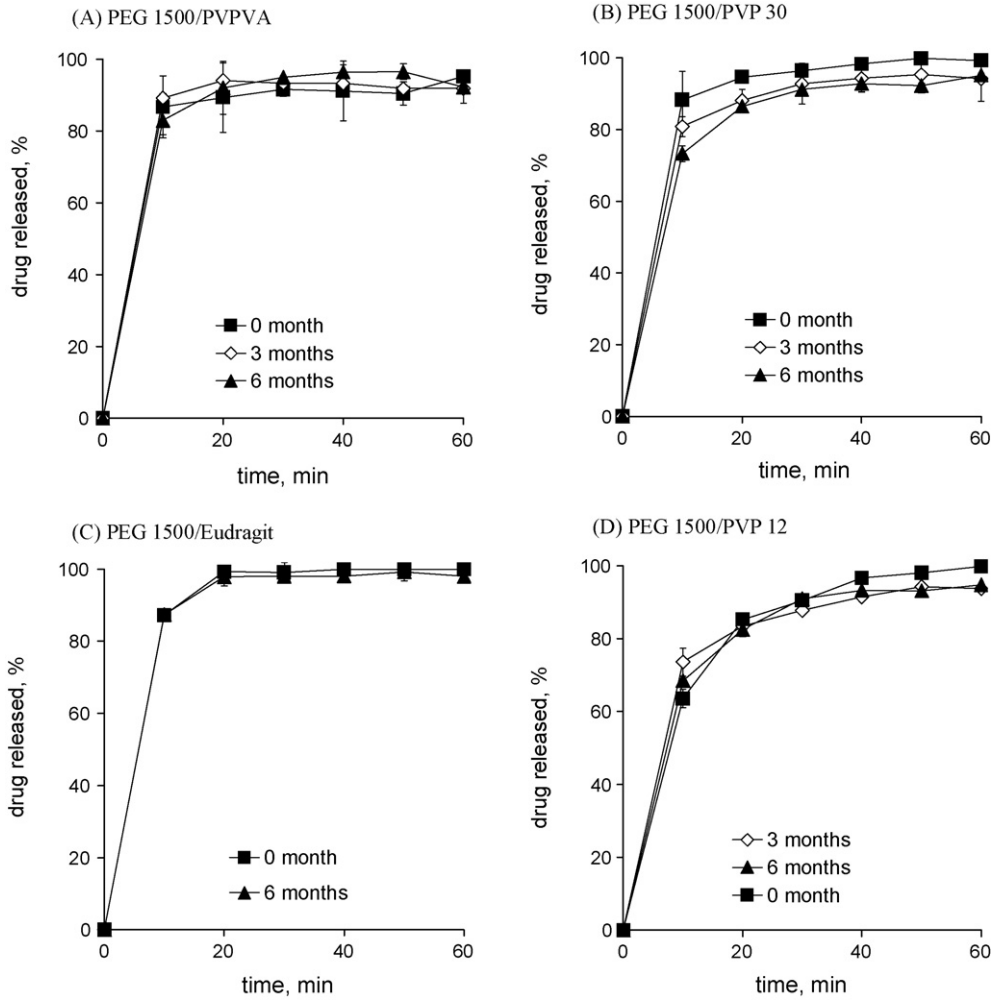


Fig. 4. Influence of polymers on the drug release from carbamazepine/PEG 1500/polymer solid dispersions after preparation (0 month) and storage for 3 and 6 months at 25 °C/0% RH: (A) PVPVA, (B) PVP 30, (C) Eudragit, (D) PVP 12.

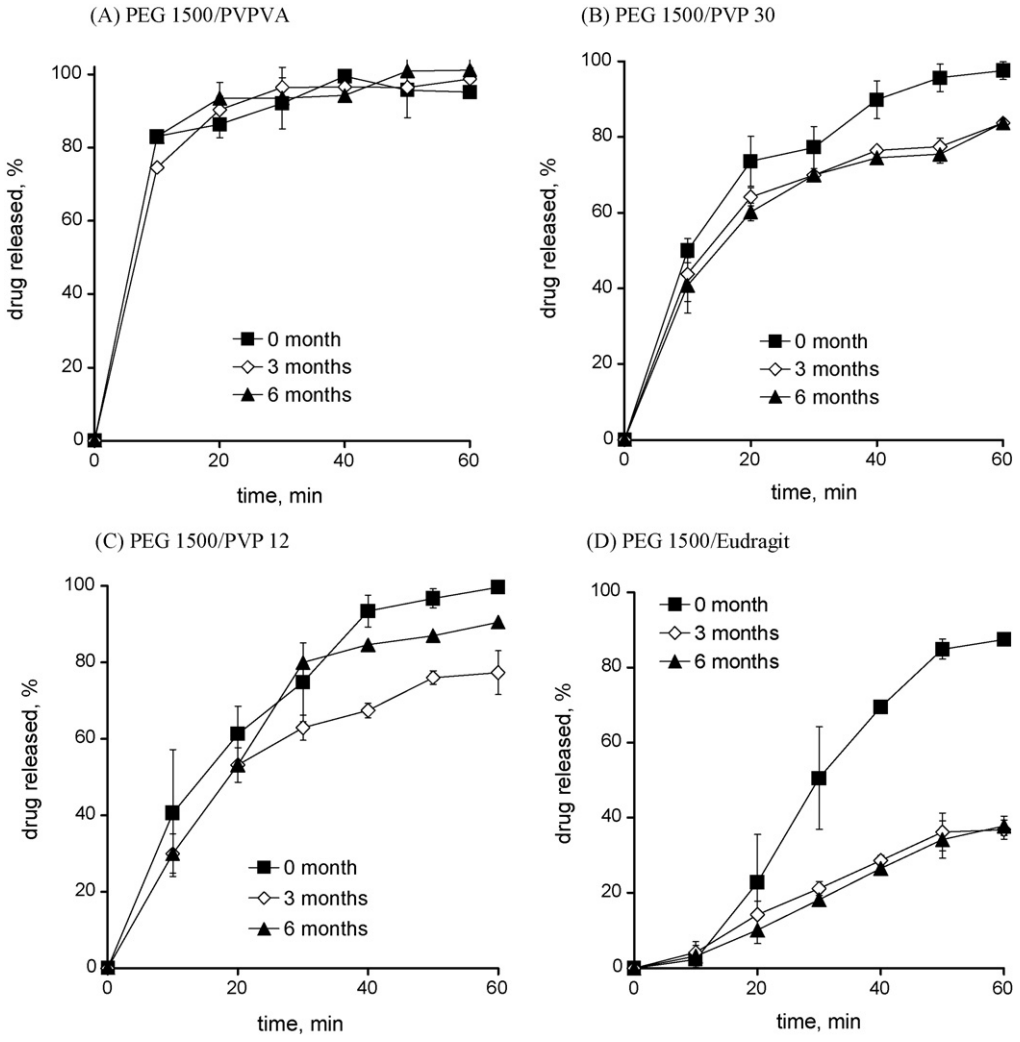


Fig. 5. Influence of polymers on the drug release from nifedipine/PEG 1500/polymer solid dispersions after preparation (0 month) and storage for 3 and 6 months at 25 °C/0% RH: (A) PVPVA, (B) PVP 30, (C) PVP 12, (D) Eudragit.

after 3 or 6 months storage at 25 °C/0% RH (Fig. 2A and B). The release from the nifedipine solid dispersions was more reduced when compared to the release from the carbamazepine solid dispersions, probably because of the lower solubility of nifedipine ($Cs_{nifedipine} = 10 \pm 3$ μg/ml, $Cs_{carbamazepine} = 240 \pm 5$ μg/ml at 25 °C in water). The nearly unchanged X-ray profiles with time led to the conclusion that the reduced dissolution rates were not caused by a significantly higher crystallinity of the drugs within the solid dispersions (Fig. 3). Observations under the polarized microscope and the X-ray diffraction data suggested that the drug was partially dissolved and partially present as small crystallites and amorphous particles within the PEG 1500 carrier.

PEG 1500 formulations were stabilized by the addition of a third component such as surfactants (Mura et al., 1999). In this study, the addition of a second polymer, which could potentially inhibit the drug recrystallization, to the PEG 1500 formulation, was investigated. The miscibility of PEG 1500 and the polymers PVPVA, PVP 30, PVP 12 and Eudragit was tested in preliminary experiments in order to choose suitable carrier combinations. 1:1 mixtures of PEG 1500 and the polymer melted at 140 °C were less viscous than the pure polymers (Friedrich, 2004). The PEG 1500/PVP 30 melts were more viscous than the other mixtures, due to the higher molecular weight of PVP 30. The drugs were easily dispersible in the molten blends of PEG 1500/PVPVA, PEG 1500/PVP 12 and PEG 1500/Eudragit at 140 °C. Clear and homogeneous drug: carrier melts were obtained, which solidified in an opaque solid dispersion after cooling in an ice bath.

The dissolution profiles of the solid dispersions varied depending on the type of drug and the PEG 1500/polymer combination. Rapid dissolution rates of the carbamazepine solid dispersions were obtained with PEG 1500/PVPVA (86% drug dissolved within 10 min), PEG 1500/PVP 30 (88%) and PEG 1500/Eudragit (87%) (Fig. 4A–C). In contrast, only 64% of carbamazepine was released from the PEG 1500/PVP 12 solid dispersion within 10 min (Fig. 4D). This could be caused by the lower amount of dissolved carbamazepine within the PEG 1500/PVP 12 carrier and probably a higher recrystallization tendency compared to the PEG 1500/- PVPVA and -PVP 30 carriers (Friedrich, 2004).

Large differences in release were seen with nifedipine dispersions. The nifedipine release was in the order of PEG 1500/PVPVA (83% drug dissolved within 10 min) > PEG 1500/PVP 30 (50%) > PEG 1500/PVP 12 (41%) (Fig. 5A–C). PEG 1500/Eudragit solid dispersion released only 2% nifedipine within the first 10 min (Fig. 5D).

X-ray spectra showed halo patterns for PEG 1500/PVPVA and PEG 1500/PVP 30 solid dispersions with carbamazepine and for all PEG 1500/polymer solid dispersions with nifedipine, which indicated that both drugs were obviously present in an amorphous and/or partially dissolved form (Fig. 6). The crystallinity of carbamazepine was higher in the PEG 1500/PVP 12 and PEG 1500/Eudragit solid dispersions. Decreasing the amount of PEG

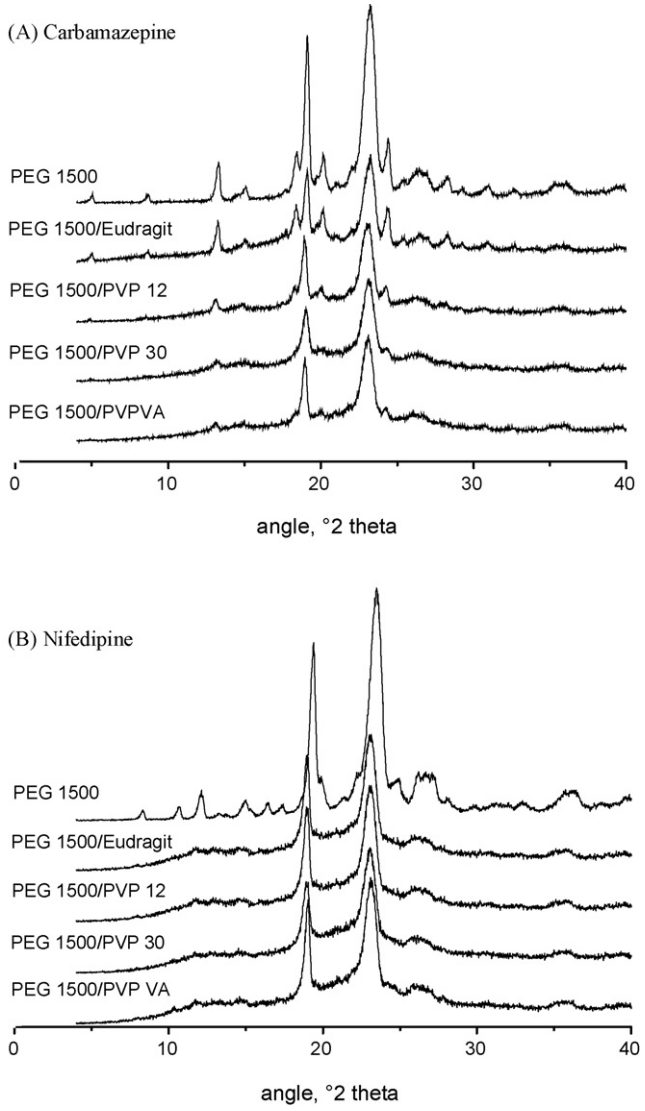


Fig. 6. X-ray patterns of drug/PEG 1500/polymer dispersions: (A) carbamazepine, (B) nifedipine.

1500 and increasing the amount of PVP or PVPVA resulted in the precipitation of partly crystalline nifedipine after solidification of the molten blends, as shown for nifedipine and PEG 1500/PVPVA (Fig. 7). DSC-studies showed, that approximately 40% (w/w) carbamazepine of drug load were dissolved in molten PEG 1500, 25% (w/w) in PVP 30, 45% (w/w) in PVPVA and 60% (w/w) nifedipine in PEG 1500, 5% (w/w) in PVP 30, 35% (w/w) in PVPVA (Friedrich, 2004). DSC measurements on the solid dispersions resulted in the dissolution of the drugs in the melted carriers during the test run and therefore gave no further information about the physical state of the drug.

However, a direct correlation between increased dissolution rate and decreased crystallinity was not found. For carbamazepine solid dispersions, a correlation between crystallinity/dissolution/solubility in the carrier and dissolution rate existed for the PEG 1500/PVP 12 solid dispersions, which had the lowest dissolution rate (64% drug within 10 min) and a higher crystallinity and lower drug solubility in the carrier compared to the PEG 1500/PVP 30 (88%) and PEG 1500/PVPVA (86%) solid dispersion, which contained a higher amount of amorphous/dissolved carbamazepine. PEG 1500/Eudragit contained the drug partially crystalline; consequently the drug release (87%) was mainly influenced by the carrier. In case of nifedipine, the enhanced drug release was caused by the physical state of the drug (amorphous in all combinations) and the carrier combination, because the dissolution was slightly different among the compositions. In summary, the dissolution rates were influenced by the type of polymer and by the amount of amorphous/dissolved drug in the carrier.

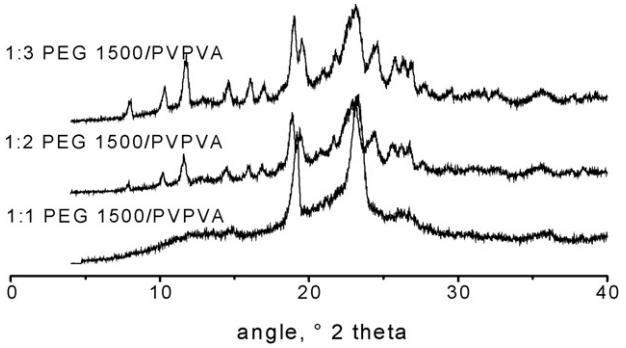
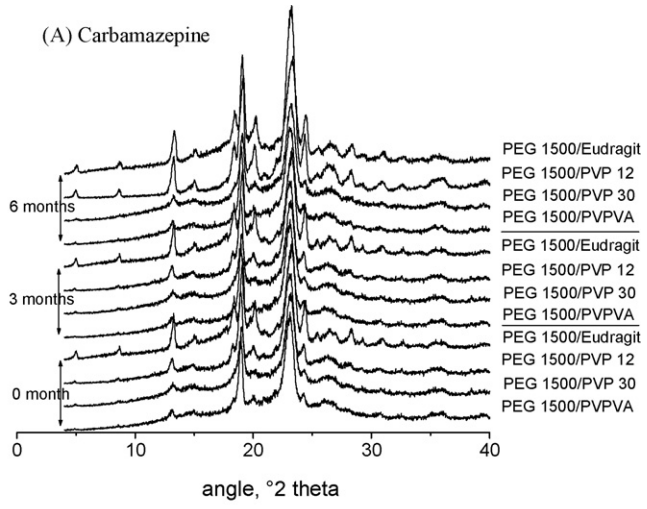


Fig. 7. Influence of PEG 1500/PVPVA ratio on the crystallinity of nifedipine.



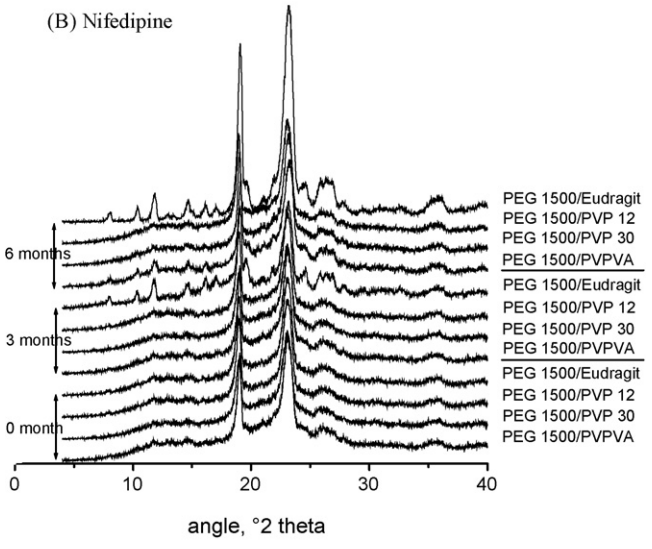


Fig. 8. X-ray patterns of drug/PEG 1500/polymer dispersions after preparation (0 month) and storage for 3 months and 6 months at 25 °C/0% RH: (A) carbamazepine, (B) nifedipine.

The carbamazepine solid dispersions with PVPVA, PVP 30, PVP 12 and Eudragit were stable for 3 and 6 months storage at 25 °C/0% RH with regard to dissolution rate and physical state of the drug (Figs. 4 and 8A). Carbamazepine showed some crystallization after 6 months within the PEG 1500/PVP 12 dispersion without influence on the dissolution rate (Figs. 4D and 8A).

With nifedipine/PEG 1500/PVPVA solid dispersions, the X-ray pattern showed an increased crystallinity after 6 months storage, however, the dissolution profile remained stable, probably because of recrystallization inhibition during contact with the dissolution medium (Figs. 5A and 8B). PEG 1500/PVP 30 and PEG 1500/PVP 12 stabilized the amorphous nifedipine (Fig. 8B), whereas the dissolution rates decreased to a small extent with storage time (Fig. 5B and C). PEG 1500/PVP 12 kept nifedipine in the amorphous state over the tested time period, whereas the dissolution rate decreased (Figs. 5C and 8B). This could be caused by a higher mobility of the drug molecules within the solid dispersion and hence a fast recrystallization tendency after contact with the dissolution medium. The nifedipine/PEG 1500/Eudragit solid dispersion was not stable. The mobility within the solid dispersion was probably increased, causing the slower dissolution rate after 3 months (Fig. 5D). After 6 months, the mobility of nifedipine within the solid dispersion was high enough to recrystallize (Fig. 8B).

Next, the influence of different solubilisers on the enhancement and stabilization of the dissolution characteristic of nifedipine/PEG 1500/PVP 30 dispersions was tested. Nifedipine was chosen because of its lower solubility and release rate. The rationale behind adding a surfactant was to increase the dissolution rate due to a higher solubilisation of the drug. All PEG 1500/PVP 30/solubiliser solid dispersions showed increased dissolution rates and stable release profiles compared to the solubiliser-free PEG 1500/PVP 30 solid dispersion (Fig. 9 vs Fig. 5). Pluronic released 85% nifedipine within 10 min, Cremophor 80% and Solutol 79% from the PEG 1500/PVP 30/solubiliser solid dispersions compared to only 50% nifedipine from the solubiliser-free PEG 1500/PVP 30 solid dispersions. The crystallinity of nifedipine was low in the solid dispersions with Cremophor, Pluronic and Solutol (Fig. 10). After 6 months storage, the crystallinity in solubiliser-containing solid dispersions was not higher than that in the solubiliser-free solid dispersion.

One disadvantage of the investigated polymers, PVP, PVPVA and also PEG 1500 for the preparation of solid dispersions are their hygroscopic properties. This could be detrimental for systems containing amorphous drugs because of possible drug recrystallization upon moisture exposure. The PEG 1500/polymer solid dispersions of both drugs underwent a phase separation in less than 3 months when stored at 40 °C/75% RH, as exemplified with carbamazepine (Fig. 11). The PEG 1500/polymer solid dispersions with PVP 30, PVP 12 and PVPVA, showed two phases, when stored as powders in vials, with the clear phase being the PEG 1500 phase and the turbid phase being the PVP- or PVPVA-rich phase.

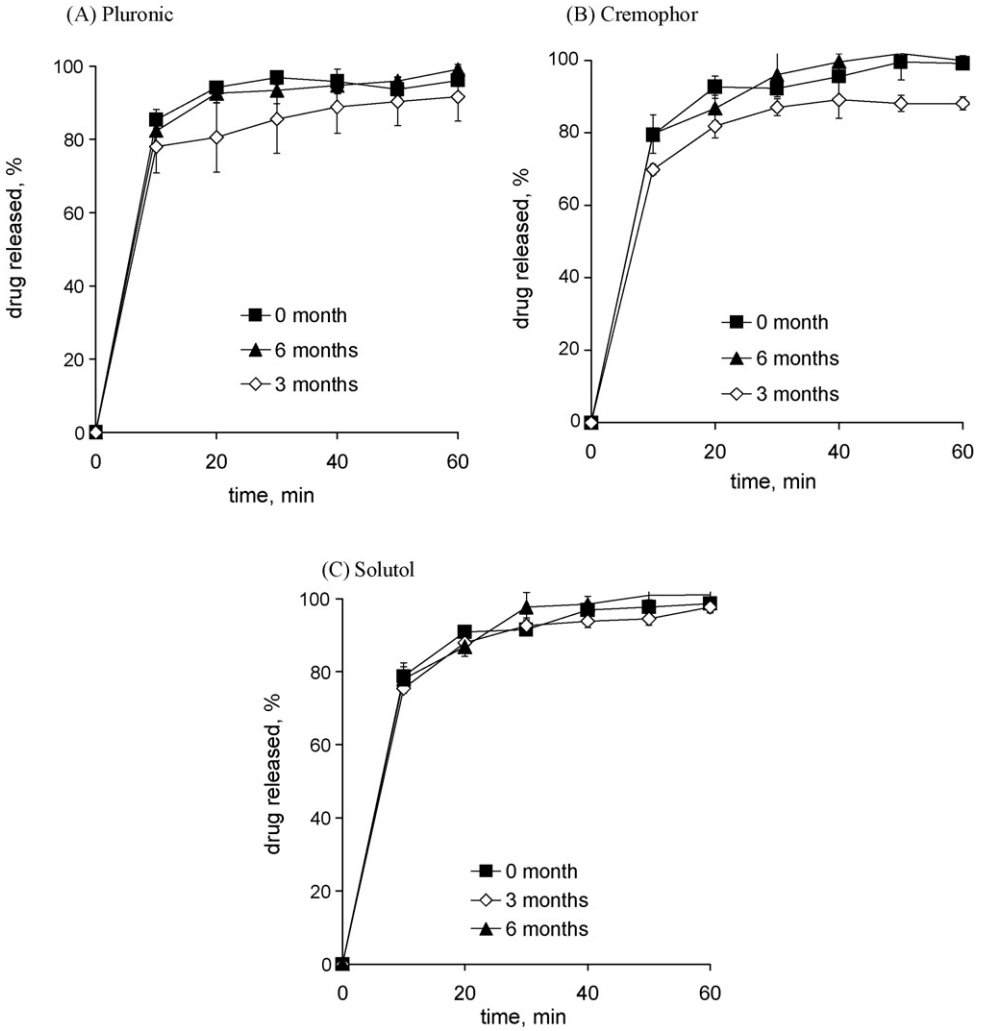


Fig. 9. Influence of the addition of solubilisers on the drug release from nifedipine/PEG 1500/PVP 30 solid dispersion after preparation (0 month) and storage for 3 and 6 months at 25 °C/0% RH: (A) Pluronic, (B) Cremophor, (C) Solutol.

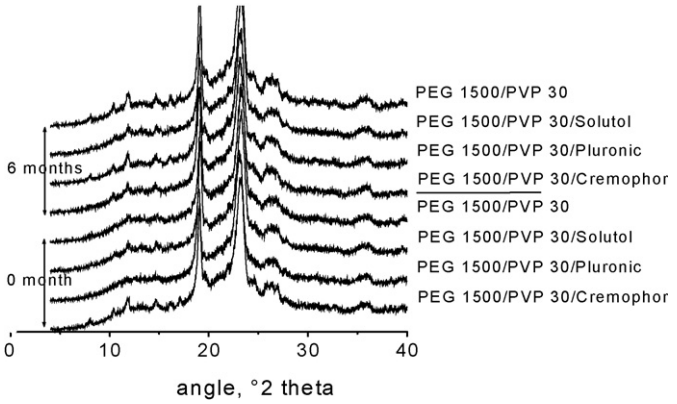


Fig. 10. X-ray patterns of nifedipine/PEG 1500/polymer/solubiliser dispersions after preparation (0 month) and storage for 3 months and 6 months at 25 °C/0% RH.

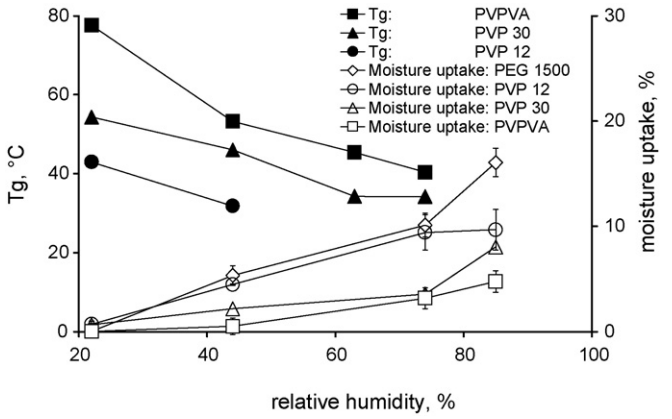


Fig. 12. Influence of relative humidity on the glass transition temperature (Tg) (closed symbols) of PVPVA, PVP 30 and PVP 12 stored for 9 days and on the moisture uptake (empty symbols) of PEG 1500, PVPVA, PVP 30 and PVP 12 after 7 days.

No drug crystals were found in the clear liquefied PEG 1500 phase under the polarized light microscope, suggesting that the drug was amorphous or dissolved in the PEG 1500 phase. The turbid, weak yellow appearance of PVP- or PVPVA-rich phases could be caused by the amorphous drug form, because no drug crystals were found in these phases under the microscope. In summary, the phase separation induced by the water uptake was not detrimental for the stability of the amorphous drugs, because the X-ray diffraction measurements still indicated halo patterns (not shown). The PEG 1500/Eudragit dispersion did not separate in two phases, however, a lumping of the powder was noticed because of the presence of the hygroscopic PEG 1500 (Fig. 11D).

The change of the appearance of the solid dispersions was related to the amorphous PVP or PVPVA going through their glass transition upon water uptake (Kieckens et al., 2000). When PEG 1500 and the polymers were stored at higher relative humidities, their physical states changed from a powder to a gel and then to a liquid. The transition increased with decreasing molecular weights of the PVPs. PVP 12 swelled already after 1 day storage at 63% RH and PVP 30 formed a wet powder after 4 days. PVPVA swelled, when stored at 74% RH. Eudragit remained a dry powder at all relative humidities, thus revealing its less hygroscopic nature. The moisture uptake of the polymers increased in the order Eudragit < PVPVA < PVP 30 < PVP 12 < PEG 1500 (Fig. 12). A higher moisture uptake resulted in a lower Tg. The exposure to moisture depressed the Tg of PVPVA (117 °C), PVP 30 (179 °C) and PVP 12 (110 °C) to below the storage temperature of 40 °C within 7 days. The Tg of Eudragit (56 °C) did not change at such a rate (56–53 °C) and was therefore not included.

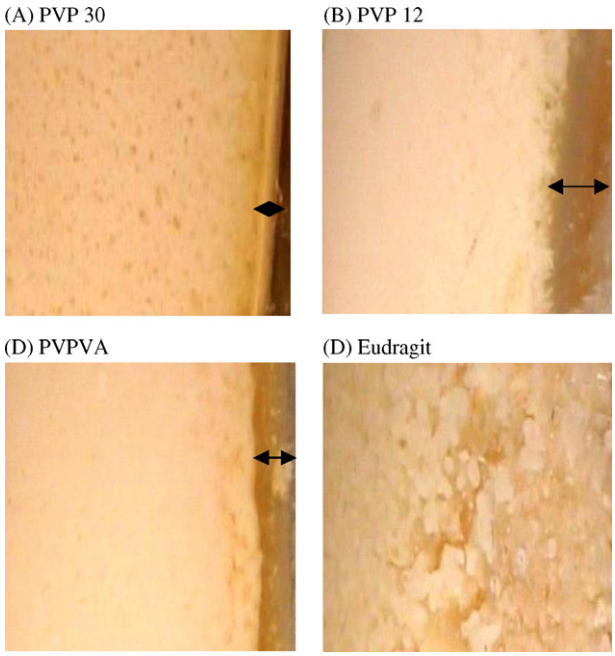


Fig. 11. Photographs of carbamazepine/PEG 1500/polymer solid dispersions stored for 3 months at 40 °C/75% RH: (A) PVP 30, (B) PVP 12, (C) PVPVA, (D) Eudragit.

4. Conclusion

Solid dispersions with PEG 1500 increased the dissolution rates of both drugs, but were unstable during storage. The combination of PEG 1500 and the higher melting amorphous polymers PVP 30, PVP 12, PVPVA and Eudragit allowed the preparation of solid dispersion by the melting method. The most stable solid dispersion concerning dissolution rate and stable amorphous drug was the drug/PEG 1500/PVPVA solid dispersion for both drugs followed by the PEG 1500/PVP 30, PEG 1500/PVP 12 and PEG 1500/Eudragit solid dispersions. An addition of a solubiliser to the PEG 1500/PVP 30 solid dispersions increased the dissolution rate of nifedipine compared to the PEG 1500/PVP 30 solid dispersion, mainly due to the improved solubilisation activity of the carrier mixture.

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