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A multiparticulate drug-delivery system based on pellets incorporated into congealable polyethylene glycol carrier materials

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Abstract

As a novel alternative to the incorporation into hard gelatin capsules or tablets, extended-release (Aquacoat®- or Eudragit® RS-coated) or enteric (Eudragit® L-coated) pellets were embedded into congealed tablet-shaped PEG-plugs of different molecular weights, which rapidly released the pellets upon contact with aqueous fluids. The lower-molecular-weight PEGs (600 and 1000) were not suitable carrier materials: they dissolved the coatings or significantly increased their permeability. The release characteristics of the original pellets were maintained after embedding the pellets into the higher-molecular-weight PEGs 4000 or 10 000. The shelf-life stability was a function of storage temperature and coating material. Stored at 40°C, Aquacoat®-coated pellets embedded in PEG 4000 exhibited a decreased drug release because of curing effects, while storage at 20°C or below resulted in stable release profiles over a 3 month period. Eudragit® RS-coated pellets, stored at room temperature or above, showed an increased release, and the carrier material possibly migrated into the film, thus increasing its permeability. At 4°C, the release was stable over a 6 month period. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Coating; Congealing; Multiparticulates; Pellets; Polyethylene glycol; Stability

1. Introduction

When compared with single-unit dosage forms, oral multiparticulate drug-delivery systems (e.g. pellets, granules) offer biopharmaceutical advantages in terms of a more even and predictable distribution and transportation in the gastrointestinal tract, which is fairly independent of the nutritional state (Krämer and Blume, 1994). In contrast to single units, coated pellets can be used to mix incompatible drugs or to tailor the overall release of the delivery system by combining pellets with different release patterns (Ghebre-Sellassie, 1989).

Controlled release pellets are usually filled into hard gelatin capsules or are compressed into tablets as the final dosage forms (Bodmeier, 1997). These dosage forms have several disadvan-

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tages, like the risk of tampering with capsules or the rupturing of the coating during compression resulting in a loss of the controlled drug-release properties (Lin, 1988).

Liquid multiparticulate systems suffer from physical and chemical stability problems, like sedimentation and caking of the multiparticulates or degradation of the drug. In addition, during storage, the drug can leach into the carrier vehicle, or the release pattern can change because of interactions between the vehicle and the coating material (Bodmeier and Paeratakul, 1994). To overcome these problems, reconstitutable multiparticulates have been developed, whereby the multiparticulates are dispersed in a liquid vehicle just prior to use (Ibsen, 1990; Weiss et al., 1998).

In this study, the pellets were dispersed into molten carrier materials, which congealed into tablet-shaped plugs upon cooling within a mold. The carrier material selected was polyethylene glycol, PEG. Different grades of PEG were examined, from the semi-solid PEG 1000 to the solid PEG 4000 and 10 000 in order to obtain dosage forms of the appropriate consistency. PEGs are readily soluble in the GIT-fluids and rapidly release the incorporated pellets. Besides water-soluble PEGs, lipids, which have a melting point at body temperature, can be considered, and these liberate the pellets upon melting. Polyglycolated glycerid-derivatives (e.g. Gelucire®) with higher melting points can also be used, and these disperse in GIT fluids because of their high HLB value.

The pellets are not compressed with this novel method, and therefore, there is no risk of mechanically damaging the coating. However, there is a close contact between the carrier material and the pellet coating. The release-controlling properties of the coated pellets should not be altered by the embedding procedure. Potential problems are plasticization or, in the worst case, dissolution of the coating in the carrier, leakage of soluble film constituents (e.g. plasticizer) or drug into the carrier or chemical reactions having an impact on drug release or stability. The objective was therefore to identify carrier coating combinations, which did result in a rapid release of the pellets from the congealed matrix and resulted in unchanged drug release profiles during storage.

2. Materials and methods

2.1. Materials

The following chemicals were used as received: chlorpheniramine maleate (CPM; Thiemann Arzneimittel, Waltrop, Germany), theophylline pellets (94% w/w drug content; Klinge Pharma GmbH, Munich, Germany), non-pareil pellets (Nu-pareil PG sugar spheres NF, Hanns G. Werner, Tornesch, Germany), Aquacoat® ECD-30 (FMC, c/o Lehmann and Voss & Co., Hamburg, Germany), Eudragit® RS 30D and Eudragit® L 30D (Röhm GmbH, Darmstadt, Germany), triethyl citrate (TEC) and acetyltributyl citrate (ATBC; Morflex, Greensboro, NC), polyethylene glycol (PEG) 600, 1000, 4000, 10 000, the numbers referring to the average molecular weight (BASF, Ludwigshafen, Germany).

2.2. Coating of drug-containing pellets

The pellets were prepared as described in detail elsewhere (Wesseling and Bodmeier, 1999). In brief, CPM was layered onto nonpareil pellets (resulting in 12% w/w drug loading) and subsequently coated in a fluidized bed coater (GPCG 1, Wurster insert, Glatt GmbH, Binzen, Germany). The aqueous polymer dispersions were mixed with either TEC or ATBC as plasticizers (20% w/w, based on the polymer) and were diluted to a polymer content of 15% w/w with water prior to coating. The coating level was 10% w/w for the CPM-containing pellets. Theophylline pellets were coated alike, with a 7.5% w/w coating level. Gastric-resistant theophylline pellets had a 10% w/w Eudragit® L coat (plasticized with 20% w/w TEC based on the polymer).

2.3. Incorporation of the pellets in the carrier

The complete dosage form was prepared by pouring the molten carrier alternately with the pellets into a Teflon mold with cylindrical cavities. To prevent sedimentation and to reduce the thermal strain of the pellets, the PEG layers were allowed to cool down and solidify before adding

further pellets. The resulting matrices contained only 8–12% w/w pellets in order to maximize potential interactions between the carrier and the pellets. They were stored in the molds, covered with Parafilm®, under ambient conditions (approx. 20°C, 50% R.H.) until further experimentation (5 or 10 days).

For stability studies, the pellet-containing matrices were wrapped into aluminum foil and stored for 3–6 months in a closed screw capped plastic jar at room temperature (20°C), in a refrigerator (4°C) or in a climatic chamber at 40°C and 75% R.H. (Weis Umwelttechnik Typ 125SB/410IU, Lindenstruth, Germany).

2.4. In-vitro release studies

The USP XXIII rotating paddle method (VanKel 700, VanKel Industries, Edison, NJ, USA; 900 ml 0.1 N HCl, 37°C, 75 rpm) was used to study drug release ($n = 2–4$). Samples were withdrawn automatically after predetermined time intervals through filters. After 24 h, the pellets were crushed by an Ultra-Turrax® (Janke and Kunkel GmbH, Staufen, Germany) and stirred for another hour at 150 rpm to determine the total amount of drug. With the enterically coated pellets, 0.1 N HCl was replaced after 2 h with 0.1 M phosphate buffer pH 7.4 USP XXIII. Disintegration of the coating was confirmed macroscopically. Theophylline and CPM were detected by UV spectrophotometry (UV-2101PC, Shimadzu Europa GmbH, Duisburg, Germany) at 270 and 264 nm.

3. Results and discussion

3.1. Aquacoat®-and Eudragit RS® 30D-coated pellets

The major challenge with the congealable carrier system was to obtain a drug-delivery system that rapidly released the incorporated pellets with their original properties, in particular, with unchanged drug release patterns. Polyethylene glycols (PEGs) 4000 and 10 000 yielded congealed plugs with good mechanical properties and a good water miscibility. For the pellet systems, two widely used aqueous polymer dispersions, Aquacoat® (ethylcellulose) and Eudragit® RS 30D [poly(ethylacrylate, methyl-methacrylate trimethyl-ammonio-ethylmethacrylate chloride 1:2:0.2] were used as polymeric coating materials. The polymers were plasticized with either the water-soluble plasticizer, triethyl citrate (TEC) or the water-insoluble plasticizer, acetyltributyl citrate (ATBC). Theophylline and CPM were used as model drugs with different water solubilities. The pellets showed a stable release pattern, and no changes were observed upon 12 months' storage at ambient conditions.

The release from Aquacoat®/ATBC-coated theophylline pellets incorporated in different PEGs after a storage time of 5 or 10 days is shown in Fig. 1a. Pellets that were suspended in liquid PEG 600 for 5 days showed no sustained, but an immediate drug release. The drug release from pellets embedded into the semi-solid PEG 1000 increased markedly after storage for 5 days and even more after a storage time of 10 days. The lower-molecular-weight PEGs were therefore not suitable as vehicles for the pellets, they interacted strongly with the polymeric coating. Ethylcellulose is soluble in PEG 600, which therefore dissolved the Aquacoat® films, thus explaining the burst release. PEG 1000 also dissolved the polymer coatings, but more slowly. In addition, the semi-solid PEG 1000 did not form plugs of sufficient mechanical stability. In contrast, incorporating the pellets into higher-molecular-weight solid PEG 4000 or 10 000 plugs resulted in similar release profiles to those of the original pellets. The congealed plugs were of sufficient mechanical strength.

Similar results were obtained with Aquacoat®-coated pellets plasticized with the water-soluble plasticizer, TEC, instead of the water-insoluble plasticizer, ATBC (Fig. 1b). Incorporating the pellets into PEG 4000 plugs resulted in stable release profiles. PEG 4000 was also a suitable carrier for chlorpheniramine maleate (CPM)-containing pellets coated with Aquacoat®. The release profiles were unchanged after incorporation into the PEG 4000 plugs (Fig. 2a and b). CPM was released faster than theophylline (Fig. 1), even at

a higher coating level (10 vs. 7.5% coating level). The faster release was caused by its higher water solubility and an osmotically active core (non-pareil sugar pellets vs. high theophylline-loaded pellets).

Besides ethylcellulose (Aquacoat®), polymethacrylates, such as Eudragit® RS, a poly(ethylacrylate, methyl methacrylate) derivative with quaternary ammonium groups, are widely used as controlled release membranes for pellets (Lehmann, 1997).

Similar to ethylcellulose, Eudragit® RS was dissolved in PEG 600 and at a slower rate also in PEG 1000. This was reflected in the dissolution data, and theophylline was released rapidly from the embedded pellets (Fig. 3a and b). With

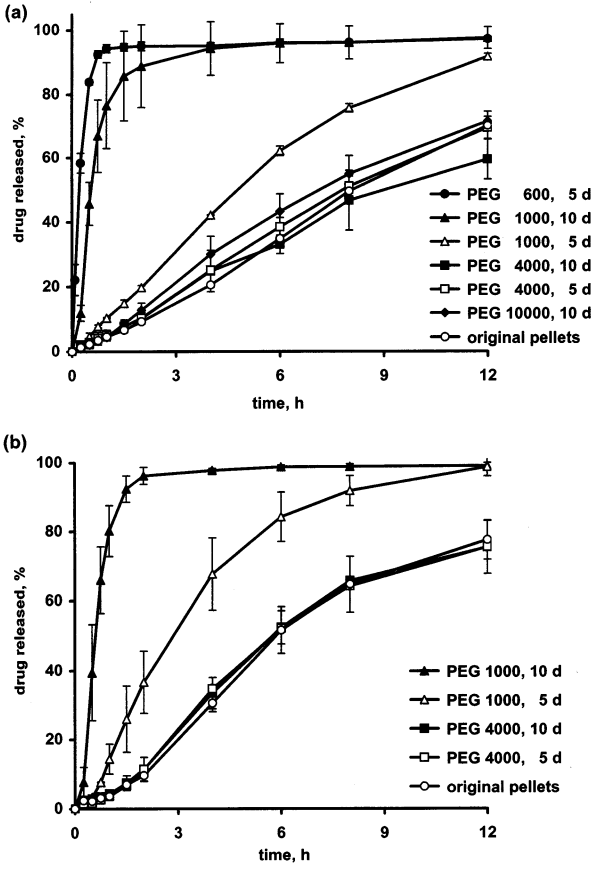

Fig. 1. Effect of PEG-type on the theophylline release from pellets coated with (a) Aquacoat®/ATBC or (b) Aquacoat®/TEC after 5 or 10 days' storage.

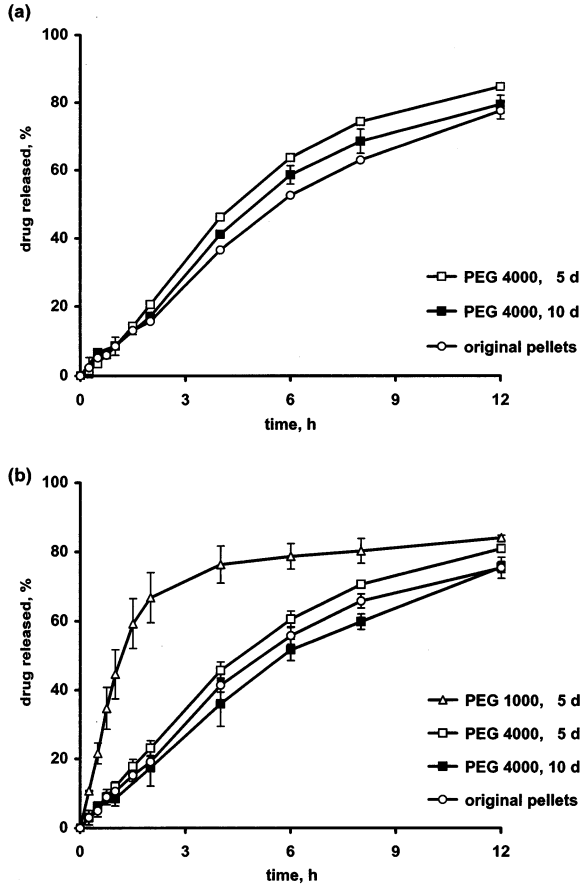

Fig. 2. Effect of PEG-type on the chlorpheniramine maleate release from pellets coated with (a) Aquacoat®/ATBC or (b) Aquacoat®/TEC after 5 or 10 days' storage.

ATBC, the water-insoluble plasticizer, almost no drug was released at a coating level of 7.5% (Fig. 3a), and the use of the hydrophilic TEC resulted in faster release profiles (Fig. 3b). Pellets incorporated into PEG 4000 or 10 000 kept the original release for both the ATBC- and TEC-containing systems. PEG 6000 had no impact on the minimum film formation temperature (MFT) or T_g (glass transition temperature) of Eudragit® RS (Lehmann, 1997), the higher-molecular-weight PEGs therefore did not act as plasticizers for the polymer and did not affect the drug release.

Similar results were obtained for CPM-Eudragit® RS systems. The high-molecular-weight PEGs resulted in only small changes in the drug-release profiles (data not shown).

3.2. Enterically coated pellets

Besides polymers, which result in pH-independent drug release along the gastrointestinal tract, enteric polymers are frequently used. One of the most popular enteric polymers is Eudragit® L [poly(methacrylic acid, ethylacrylate) 1:1]. Eudragit® L 30D-coated pellets were incorporated into various PEGs, and the release was investigated for 2 h in 0.1 N HCl followed by pH 7.4 phosphate buffer. The requirements of the USP XXIII for enterically coated dosage forms (< 10% drug released in 2 h) were not met with the lower-molecular-weight PEGs 600 and 1000, and a significant amount of drug was released in 0.1 N HCl (Fig. 4). PEG 600 did not dissolve the polymer, but resulted in the swelling of the polymer, and the permeability of the Eudragit® L coating therefore increased. Incorporated into PEG 4000, the pellets released less than 5% drug within 2 h in 0.1 N HCl. The coating dissolved in pH 7.4 buffer followed by a rapid drug release. Thus, PEG 4000 devices adequately maintained the solubility and permeability characteristics of Eudragit® L.

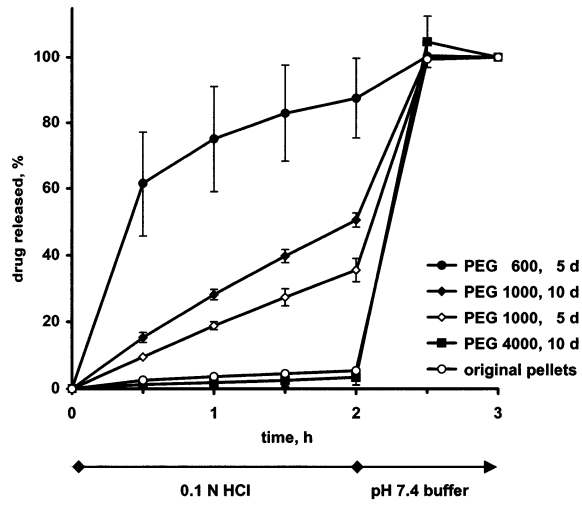

Fig. 4. Effect of PEG-type on the theophylline release from Eudragit® L/TEC-coated pellets.

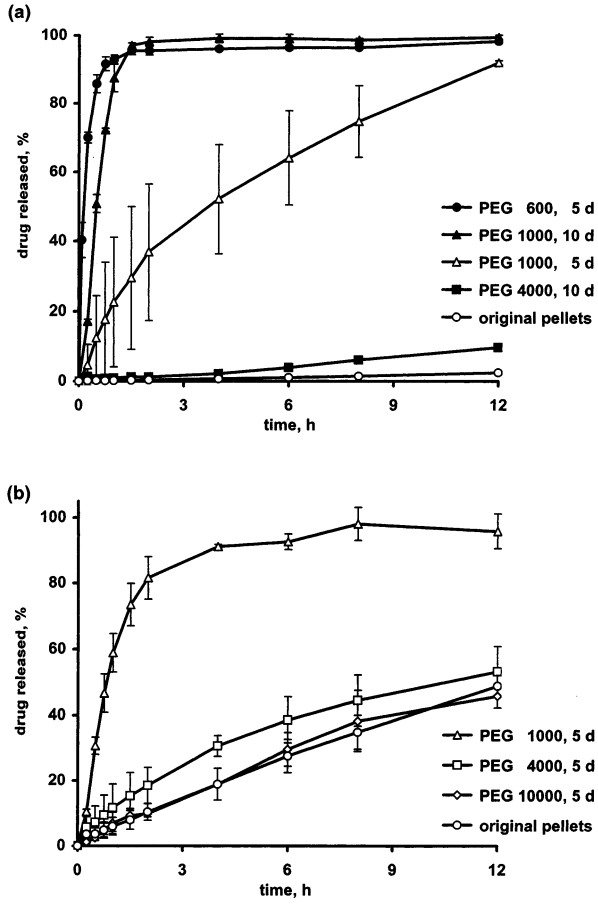

Fig. 3. Effect of PEG-type on the theophylline release from pellets coated with (a) Eudragit® RS/ATBC or (b) Eudragit® RS/TEC after 5 or 10 days' storage.

3.3. Storage stability

PEG 4000 was selected as the carrier of choice for further investigations, because PEG 10 000 resulted in brittle and therefore more difficult-to-handle preparations. PEG 4000 devices could be easily removed from the Teflon molds, had sufficient mechanical stability for processing, storage and transport, and did not interact with the pellet formulations investigated.

Accelerated stability studies over a 3 month period were performed with the pure and embedded pellets. No changes in drug release were seen after 3 months of storage under ambient conditions for theophylline pellets coated with Aquacoat®/ATBC or for the PEG-embedded pellets (Fig. 5a). Storage at 40°C, 75% R.H. led to a decrease in drug release for both embedded and

unembedded pellets. This could be explained by the further coalescence of the polymer particles of the colloidal polymer dispersion into a homogeneous film. The pellets were not cured (thermal after-treatment at elevated temperatures) directly after the coating step. The PEG matrix could be considered unaffected (T_m 50–60°C, Fiedler, 1996), but the ethylcellulose coating of the pellets was susceptible to the higher storage temperatures, and the film underwent further coalescence (Bodmeier et al., 1997). This effect and the resulting reduction in drug release were less dramatic with the PEG-embedded pellets. The coatings of the pure pellets were almost completely impermeable, while those embedded in PEG showed a reduced, but still noticeable, release.

The protecting character of PEG 4000 against temperature influences was underlined with Aquacoat®/TEC-coated pellets (Fig. 5b). Storage at or below room temperature resulted in the original release patterns. Almost no drug was released from unembedded pellets stored at 40°C for 3 months, and the coating became almost impermeable for the drug because of the continued film formation (coalescence). With pellets embedded in PEG 4000, the curing effect was less evident, and the drug release was modestly reduced. PEG 4000 therefore had a stabilizing effect on the film coating. Pellets coated with Aquacoat®/TEC were better protected than those containing the lipophilic plasticizer, ATBC. As an explanation, PEG 4000 might better protect the more hydrophilic film

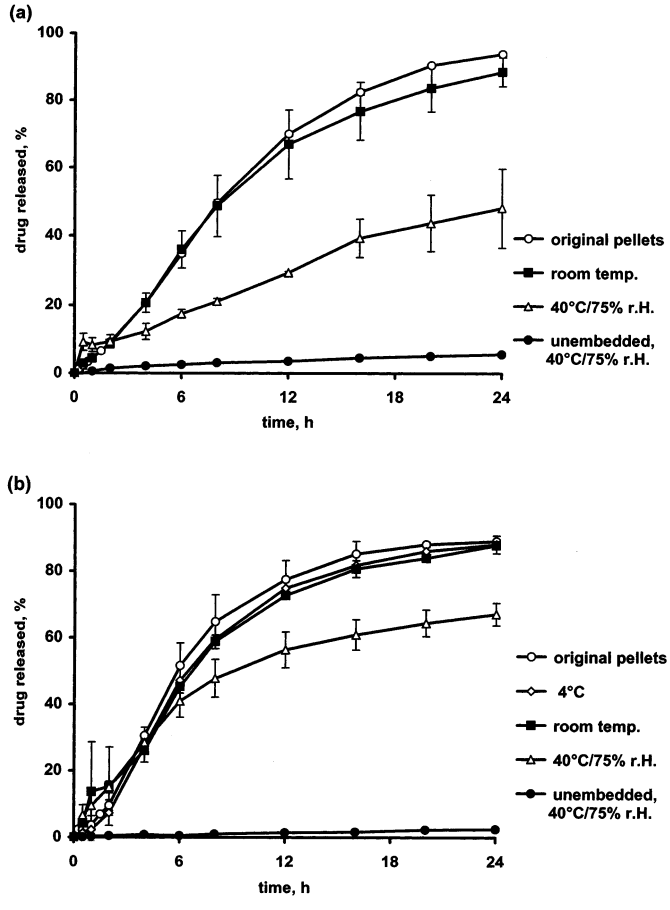

Fig. 5. Effect of storage conditions on the theophylline release from unembedded or PEG 4000-embedded pellets coated with (a) Aquacoat®/ATBC or (b) Aquacoat®/TEC.

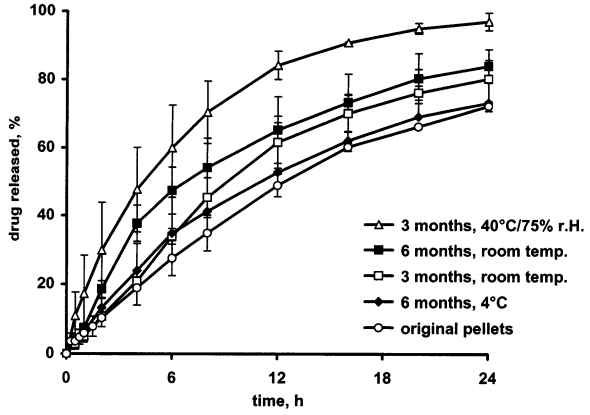

Fig. 6. Effect of storage conditions on the theophylline release from unembedded or PEG 4000-embedded pellets coated with Eudragit® RS/TEC.

(with TEC) because of a higher affinity between film and carrier. PEG 4000 could also have neutralized the decrease in permeability because of further coalescence by diffusing into the coating and therefore increasing the permeability.

In contrast to Aquacoat®-coated pellets, Eudragit® RS/TEC pellets were affected oppositely, i.e. storage at elevated temperature led to an increase in drug release (Fig. 6). Here, a potential curing effect (Ghebre-Sellassie et al., 1997) was overcome by other phenomena such as PEG migrating into the Eudragit® RS film, thereby increasing its permeability. Free pellets coated with Eudragit® RS/TEC stored at a higher temperature also showed a faster release. This could be attributed to the stickiness of the polymer coating at the higher temperature. The pellets stuck together, and the coating was damaged after separating the pellets from each other, thus explaining the rapid release. When plugs with pellets were stored at 4°C, the release was identical to that of the original pellets: the PEG obviously did not interact at lower temperatures with the polymeric coat. After storing the embedded pellets for 3 months at room temperature (20°C), an increase in release was observed. After a further 3 months, this effect was enhanced. A further increase in release rate was observed after storage at 40°C. Eudragit® RS was therefore more susceptible to the plasticization effects of the PEG 4000 than ethylcellulose. Ethylcellulose has a higher glass transition temperature and has a lower affinity for PEGs than the more hydrophilic Eudragit® RS.

In conclusion, PEG 4000 was a suitable congealable carrier material for coated controlled release pellets. Possible interactions between the coating and the carrier material could potentially be overcome by a thin overcoating, having a low affinity for the carrier material.

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