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Physical and thermal characterisation of Precirol® and Compritol® as lipophilic glycerides used for the preparation of controlled-release matrix pellets

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Abstract

Physical and thermal properties of Compritol® and Precirol® as potential lipophilic binders in melt pelletisation process for the preparation of sustained-release matrix pellets were evaluated in this study. Experimental measurements were carried out using X-ray diffractometry, differential scanning calorimetry (DSC), hot-stage microscopy (HSM) and rheological measurements. These studies have shown that the lipophilic binders may present a relatively complex behaviour depending on the sample treatment (untreated, freshly solidified, aged samples). DSC and HSM methods have shown the presence of polymorphism for Precirol. Moreover, both untreated and fresh solidified Precirol and Compritol samples present partially amorphous layered structure which slowly crystallise in time. The rate of crystallisation was found to be more rapid for Precirol, and highly dependent on the ageing conditions (storage temperature). Finally, the evaluation of the thermal and rheological properties of Precirol and Compritol mixtures have shown that the use of such mixtures, presenting well distinct melting properties, could be a very interesting tool for the preparation of high fatty binder content prolonged-release pellets in high shear mixers if the product temperature is carefully controlled (between 45 and 50 °C) during the pelletisation process.

Keywords: Glycerides; Compritol; Precirol; DSC; X-ray diffraction; HSM; Rheology

1. Introduction

Glycerides are a family of excipients which have generated considerable interest for the preparation of oral dosage forms. Gelucires represent a wide range of meltable excipients, which are composed of mixtures of glycerides and fatty acid esters of polyethylene glycol (PEG) (Sutananta et al., 1995a). The nature and the proportion of these components determine the hydrophilic–lipophilic characteristic (HLB value) of these excipients and the drug release properties from the corresponding dosage forms (Ratsimbazafy and Brossard, 1991; Craig, 1996).

In particular, Compritol® or glyceryl behenate and Precirol® or glyceryl palmito-stearate can be used as glyceride bases for the preparation of sustained-release dosage forms (Saraiya and Bolton, 1990). Indeed, the esterification of glycerol by long chain fatty acids and

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the absence of PEG esters give them a pronounced hydrophobic character expressed by the low HLB value of 2.

Several techniques have been used to obtain prolonged-release dosage forms from glyceride-based formulations, i.e. thermoplastic or melt granulation (Saraiya and Bolton, 1990), melt pelletisation (Hamdani et al., 2002), hot-melt extrusion (Liu et al., 2001) and hot-melt coating (Barthelemy et al., 1999).

As discussed in a previous work (Hamdani et al., 2002), phenylephrine hydrochloride, ciprofloxacine hydrochloride, ketoprofen and theophylline were used as model drugs, showing very different solubility characteristics, to prepare controlled-release pellets in high shear mixer by the melt pelletisation process. In summary, lipidic formulations based on the use of appropriate mixtures of lower (Precirol®) and higher (Compritol®) melting range fatty binders were proposed. Depending on the physico-chemical properties of the active ingredient, formulations containing different blends of lactose 450 mesh and relatively high amounts of lipidic binders (up to 80%, w/w) have been used in order to obtain appropriate prolonged-release properties.

Due to their chemical and physical complexity, the lipophilic binders may exhibit a complex behaviour (i.e. melting and crystallisation, physical modifications on storage). The aim of this study is to evaluate the physical, chemical and mechanical properties of these materials. This evaluation is particularly useful for the development of such controlled-release formulations as the melting and rheological characteristics of fatty binders are the most critical parameters to consider, specially when high amount of lipidic binder mixtures are used (Hamdani et al., 2002). Moreover, the physical ageing effects associated with glyceride-based dosage forms have also to be well understood in order to avoid any further drug release alteration during storage.

Many studies (Laine et al., 1988; Sutananta et al., 1994, 1995b) have shown the importance of considering the chemical composition and the physical structure of glyceride bases in order to understand the dissolution behaviour of drugs from these systems. However, the number of effective methods available for the study of the physical structure of complex solids is very limited (Craig, 1996). Four methods will be discussed in this paper, differential scanning calorimetry (DSC), X-ray diffraction, hot-stage microscopy (HSM) and rheological measurements (controlled stress capillary rheometer).

2. Materials and methods

Glyceryl palmito-stearate (Precirol® ATO 5, also known as Gelucire 54/02) and glyceryl behenate (Compritol® 888, also known as Gelucire 70/02) were supplied from Gattefossé (France). Compritol® and Precirol® occur as fine, white free flowing powders.

2.1. Samples preparation

Three types of samples were prepared for the physical evaluation of glyceride bases:

- *Freshly solidified (F) samples*: Samples were previously melted by heating at a temperature at least 10 °C higher than their melting point, solidified at ambient temperature, and stored for 10 h at 4 °C, in order to avoid effects due to the previous thermal history.
- *Aged (A) samples*: Samples were stored up to 1 month at 40 and 50 °C, in order to detect any physical ageing effect (structural or polymorphic changes) associated with glyceride bases.
- *Untreated (U) samples*: Samples without any special treatment (as received).

2.2. Differential scanning calorimetry

The melting behaviour of the lipophilic binders was evaluated by a Perkin-Elmer DSC-7 differential scanning calorimeter/TAC-7 thermal analysis controller (Perkin-Elmer Corp., CT, USA). Samples of about 5 mg were sealed in 50 μl aluminium pans and scanned between 0 and 80 °C (for Compritol®), or 0 and 65 °C (for Precirol®), at a heating rate of 5 °C/min.

This method was also used for studying potential interactions between the lipophilic binders by performing DSC analysis on binary mixtures of Compritol® and Precirol® using similar proportions to those described in a previous work (Hamdani et al., 2002) (Table 1).

Table 1
Binary mixtures of Compritol and Precirol used for the rheological and DSC studies

Pellet formulation	Compritol (C) (%, w/w)[a]	Precirol (P) (%, w/w)[a]	C–P mixture[b]
25% meltable binder	10	15	4–6
40% meltable binder	25	15	6–4
80% meltable binder	65	15	8–2

[a] Hamdani et al. (2002).
[b] Binary mixtures of Compritol and Precirol used for physical studies.

2.3. Hot-stage microscopy

HSM analysis was conducted using a Linkam THMS 600 hot stage (England) assembled on an Olympus-BX 60 microscope (Japan), equipped with a JVC TK-C1381 (Japan) colour video camera. The different types of samples (F, U and A) were observed under the microscope by using a scanning speed of 1 °C/min. Changes in the samples morphology (melting–crystallisation) were noted as a function of temperature. Data were imported into a computer for real-time observation and storage. Captured images were analysed using an Olympus Microimage software version 4.0.

2.4. Powder X-ray diffractometry

The X-ray diffraction patterns were also determined on freshly solidified, aged and untreated samples. Samples were exposed to a monochromatic nickel-filtered copper radiation (40 kV, 40 mA) in a wide angle X-ray diffractometer (Siemens D 5000, Germany) with 2θ angle between 5° and 60°.

2.5. Rheological measurements

The rheological properties of lipophilic binders were determined on the solid material, at different temperatures close to their melting point, using a Rheograph 2002 (Göttfert, Buchen, Germany) controlled stress capillary rheometer. Pressures as high as 2×10^8 N m^{-2} (±2000 bar) were used to produce the flow of the fatty material at a constant speed through a stainless steel capillary tube.

3. Results and discussion

Fig. 1 illustrates the DSC thermograms of untreated, freshly solidified and aged (1 week at 40 °C) Compritol® and Precirol® samples. It may be observed that, depending on the sample treatment, Precirol underwent changes as reflected by the shape of DSC

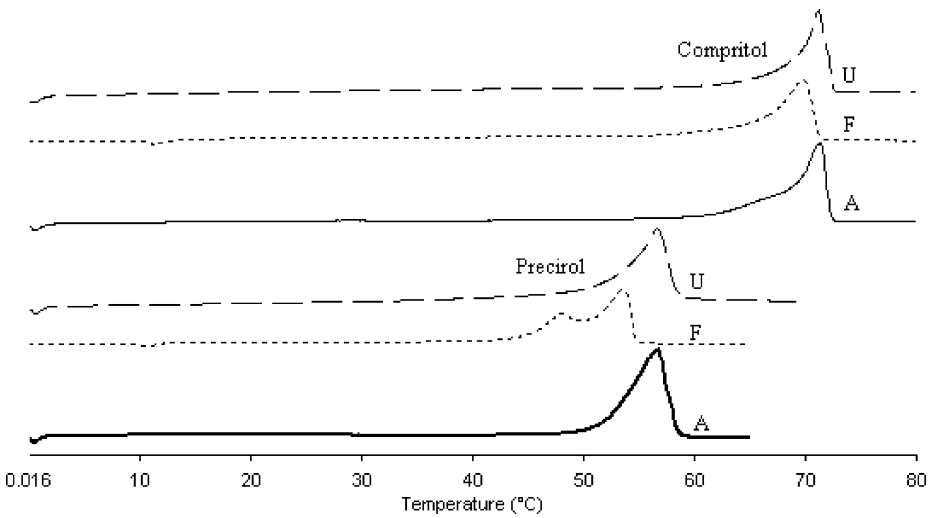

Fig. 1. DSC heating curves of Compritol and Precirol obtained from, untreated (U), freshly solidified (F) and aged (A) (stored 2 weeks at 40 °C) samples.

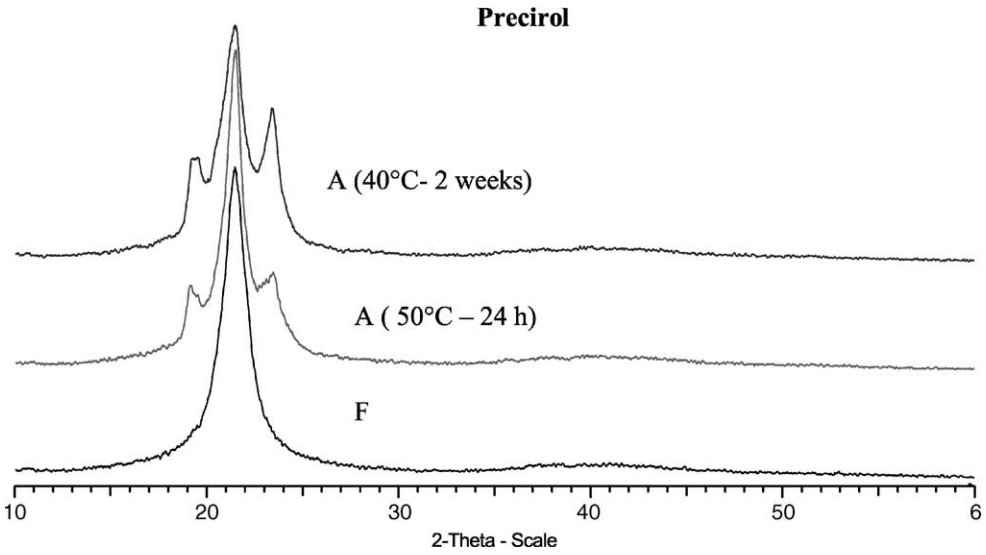

Fig. 2. X-ray diffractograms of Precirol obtained from freshly solidified (F) and aged (A) (stored 2 week at 40 °C, or 24 h at 50 °C) samples.

curves. The presence of two melting endotherms, can only be detected only on the freshly solidified sample. However, the lowest melting endotherm lost during storage go with an increase in the height and sharpness of the higher melting endotherm. These results are in accordance with those observed in a previous study by Evrard et al., 1999, in which the presence of three melting endotherms was observed by using a much faster cooling rate (around 200 °C/min.) during the sample crystallisation step. These observations demonstrate not only the importance of cooling rate during crystallisation on the sample physical state, but also the instability of some polymorphic forms of glyceride bases after crystallisation. Indeed, during these experimentations, the appearance of the low melting range endotherms of Precirol was only observed when the heating–cooling programs were applied on the samples in the DSC equipment, i.e. when DSC thermograms were performed on the freshly solidified samples immediately after crystallisation. This is probably the reason why the appearance of polymorphs of Precirol was not detected by the X-ray method (see below).

In contrast, this phenomenon was not observed for Compritol, for which DSC curves obtained are characterised by a more limited melting range, showing only one important melting endotherm at approximately 70 °C. Moreover, a careful evaluation of the DSC results obtained in Fig. 1 permits to observe that both Precirol and Compritol freshly crystallised samples show slightly lower melting endotherms in comparison with the untreated and aged samples (see discussion below).

The X-ray diffraction results shown in Figs. 2 and 3 permit to confirm the complexity of the ageing modifications observed with glyceride bases. The examination of the X-ray diffraction patterns obtained from different Precirol samples (Fig. 2) permits to observe that there is no superimposition between X-ray results obtained from the freshly solidified and aged (24 h at 50 °C and 2 weeks at 40 °C) Precirol samples. The X-ray diffraction pattern of fresh Precirol shows only one relative narrow peak at 2θ angle of 21.5°, whereas the aged samples show three peaks at 2θ angles of 19.5°, 21.5° and 23.5°. Similar modifications of the diffraction patterns were also observed for Compritol (Fig. 3). The diffraction patterns of Compritol show two peaks at 2θ angles of about 21° and 23° in all samples with the apparition of a small additional peak for the aged sample (2 weeks at 50 °C) at 2θ angle value of 19.5°. Moreover, quite same diffraction patterns as Precirol, with three well distinct and more intense peaks at 2θ angles of 19.2°, 21° and 23.5° are obtained from aged Compritol samples for longer storage times (5 weeks at 50 °C) (Fig. 3).

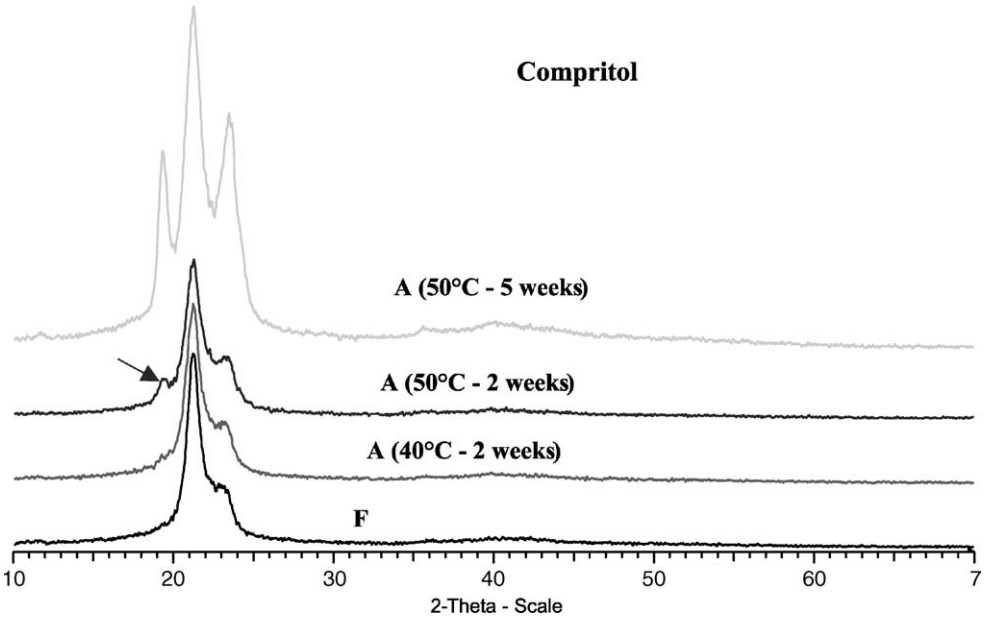

Fig. 3. X-ray diffractograms of Compritol freshly solidified (F) and aged (A) (stored 2 weeks at 40 or 50 °C, or 5 weeks at 50 °C) samples.

The examination of the DSC thermograms obtained from untreated and aged Compritol samples, submitted to the same storage conditions (Fig. 4), permit to observe that the physical modifications described above entails only a small increase of the melting endotherms after storage (from ~70 to 72 °C). Similar modifications can also be observed for Precirol samples (see Fig. 1).

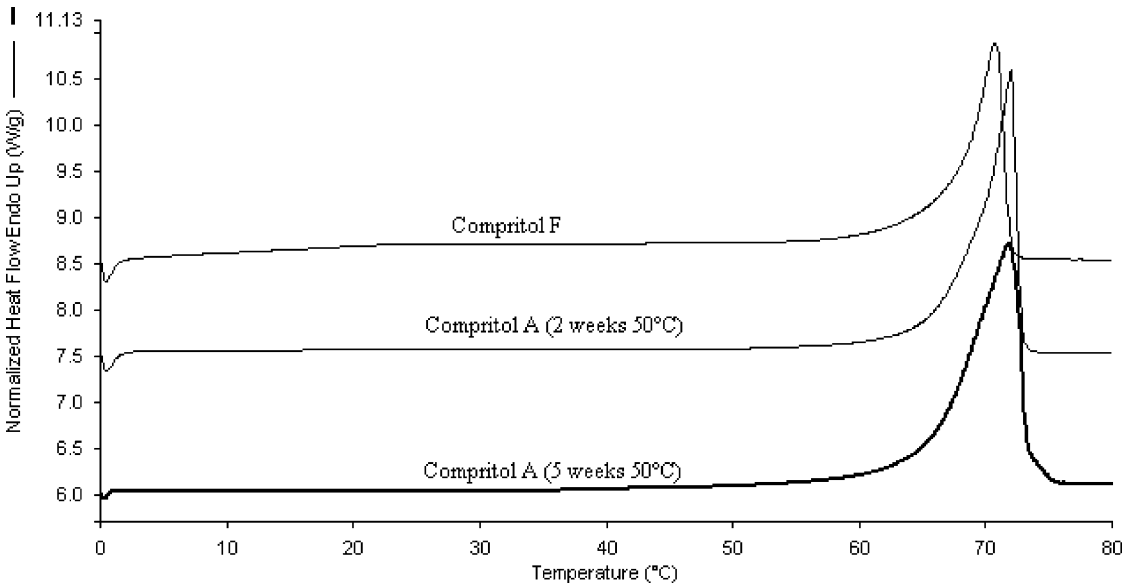

Fig. 4. DSC heating curves of Compritol, freshly solidified (F) and aged (A) (stored for 2 weeks or 5 weeks at 50 °C) samples.

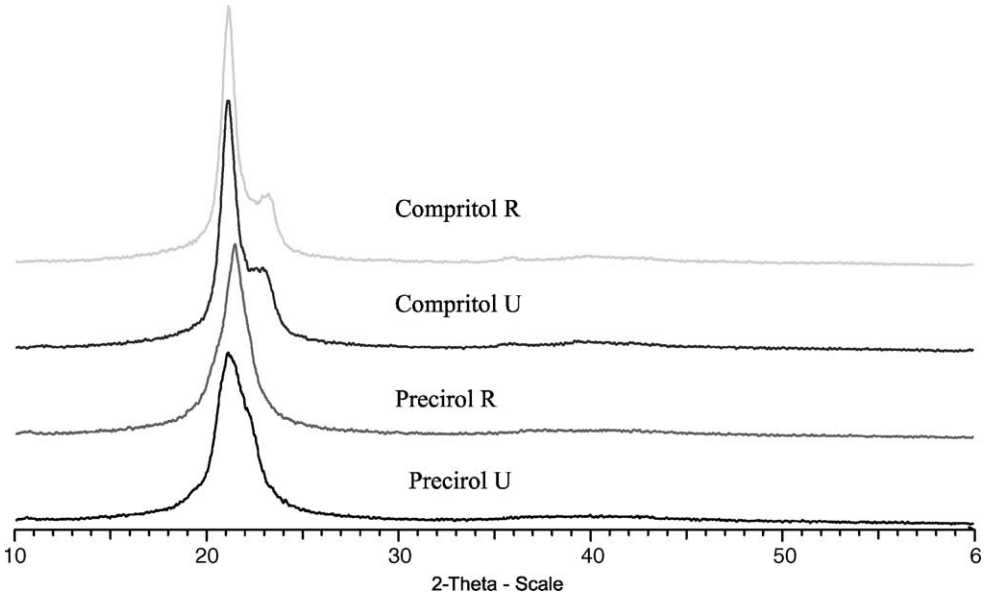

Fig. 5. X-ray diffractograms of untreated (U) and retreated (R) samples of Compritol and Precirol.

Laine et al., 1988, described similar ageing modifications in the case of triglycerides by showing that freshly solidified samples present partially amorphous layered structure which gradually crystallise during storage. Moreover, they found that the crystallisation rate depends on the size of molecules, i.e. the number of carbon atoms in the fatty acid chains. The longer is the fatty acid chain, the longer would be the crystallisation time.

In our case, the presence of this layered structure can also be observed in the diffractograms of both fresh (Figs. 2 and 3) and untreated Precirol® and Compritol® samples (Fig. 5). That means both the crystallisation conditions used for the preparation of fresh samples, and the industrial manufacturing conditions used for the preparation of commercial products (by spray congealing) promote the formation of layered structures. Moreover, the stability of the layered structures obtained for Precirol® and Compritol® seems to be substantially higher than that observed by Laine et al., 1988, for the evaluated triglycerides (tricaprin, trimyristin and tristearin), as the same layered structures are present for the untreated samples (stored as recommended by the supplier, i.e. at 4 °C) and fresh samples. Nevertheless, the crystallisation of Precirol® is obtained rapidly, after 2 weeks or 24 h, when fresh samples were stored at 40 or 50 °C, respectively (Fig. 2). The crystallisation of Compritol®, which contain longer fatty acid chain than Precirol (behenate C_{22} versus palmito-stearate C_{16}–C_{18} esters), takes remarkably more time as the layered structure disappears gradually, and a more crystalline sample appears only after 5 weeks storage at 50 °C (Fig. 3).

Finally, in order to show that the physical modifications observed are reversible, and thus to ensure that no chemical modifications occur during storage, the aged samples (after 5 weeks storage at 50 °C) were retreated by using the same thermal treatment as that used for the fresh samples (melting 10 °C above their melting point and cooling at ambient temperature), and so new resolidified samples (Compritol R and Precirol R, Fig. 5) were obtained. It can be concluded from the results obtained in Fig. 5 that there is no irreversible degradation of the structure of Compritol® or Precirol® under studied storage conditions as similar diffractograms are obtained for the untreated (U) and retreated (R) samples.

The use of lipidic excipients like glycerides suppose to consider the evolution of the crystalline properties of material on time, depending on the temperature conditions adopted during storage. Glycerides containing longer fatty acid chains and/or higher melting

range are less sensitive to such physical modifications, and thus, to the drug release rate alterations generally associated with lipidic dosage forms (Craig, 1996; Sutananta et al., 1995b).

Craig, 1996 proposed that the physical behaviour of some chemically highly complex glyceride-based products like Gelucires, may be attributed to the fractionation of the materials into microsegregated regions containing different chemical compositions; these regions contain varying compositions of the constituent molecules. Given the above considerations and despite the fact that the chemical composition of the glycerides considered in this study is much less complex than those considered by Craig, 1996, we have also used the HSM technique to understand the nature of the different physical events observed. This semi-quantitative method involves heating a sample on a hot stage and simultaneously observing the material under a microscope. Fig. 6 shows microphotographs obtained from untreated (Fig. 6a), fresh (Fig. 6b) and aged (2 weeks at 40 °C) (Fig. 6c) Precirol samples at temperature values between 42 and 58 °C. As it can be observed for the untreated sample (Fig. 6a), the majority of the fat form a liquid at 55 °C, with some small crystallites portions still visible. On the other hand, when the freshly solidified sample is reheated on the hot stage (Fig. 6b), the sample melting range temperature is substantially broader as modifications of sample structure can be observed between about 45 and 54 °C. At 58 °C the entire sample was melted for both untreated and fresh Precirol. HSM microphotographs obtained from untreated (Fig. 7a) and fresh (Fig. 7b) Compritol samples show a quite similar comportment for both samples, as the HSM microphotographs show the presence of unmelted material at 71 °C, and the totally melted one at 73 °C. These HSM observations may be correlated with the DSC results (Fig. 1), which show a narrower melting range for Compritol® than Precirol®. Moreover, as discussed before, the particular melting behaviour of the freshly crystallised sample permits to confirm the furtive apparition of polymorphic forms of Precirol (see Figs. 1 and 6a,b). An other correlation between HSM (Figs. 6c and 7c) and DSC results (Figs. 1 and 4), concern the observation that aged samples melt at slightly higher temperature values than freshly solidified samples. Indeed, HSM microphotographs permit to observe that the last crystals are still present in the observed materials at temperature values of ~55 and 72 °C, and 56 and 73 °C, for fresh and aged Precirol and Compritol samples, respectively (Figs. 6 and 7).

Finally, as the main goal of this study is the physical evaluation of lipidic excipients that have to be used as meltable binders for the preparation of controlled-release pellets in high shear mixers, the deformation properties of the unmelted Precirol and Compritol (alone or in mixture) were also studied by using a controlled stress capillary rheometer.

The rheological evaluations of Precirol and Compritol and their binary mixtures determined on the solid material at different temperatures close to their melting point, have shown a pseudoplastic flow as the log–log rheograms obtained are linear. The same proportions of glycerides as those used for the melt pelletisation process discussed in a previous work (Hamdani et al., 2002) were adopted for this evaluation. Table 1 shows the correspondence between the different Compritol–Precirol binary mixtures used for the matrix pellet formulations containing 25, 40 and 80% (w/w) meltable binders and those used in this work for the physical studies (C–P 4–6, C–P 6–4 and C–P 8–2). The apparent viscosity η_{app} results, calculated at a shear rate of 40 s^{-1}, for Compritol, Precirol and their binary mixtures at different temperatures below their melting point are summarised in Table 2 (results were completed by those obtained in a previous work Evrard et al., 1999 on each lipidic excipient alone). As can be seen, the apparent viscosity values of the unmelted lipidic binder can be determined for all mixtures at a temperature value of 50 °C. The apparent viscosity values obtained at 50 °C for the different mixtures are slightly higher than those obtained for Precirol alone, and of course, substantially lower than those obtained for Compritol alone (material too hard to be extruded). Moreover, above this temperature (between 55 and 60 °C), Precirol and the C–P 4–6 mixture, which contains the higher proportion of Precirol, become too soft because samples are practically entirely melted and thus too low viscosity values than those can be measured by such equipment were obtained. The other mixtures (C–P 6–4 and C–P 8–2) can be extruded within a wider temperature range because a major proportion of the samples stay in an unmelted form thanks to the presence of much higher proportions of

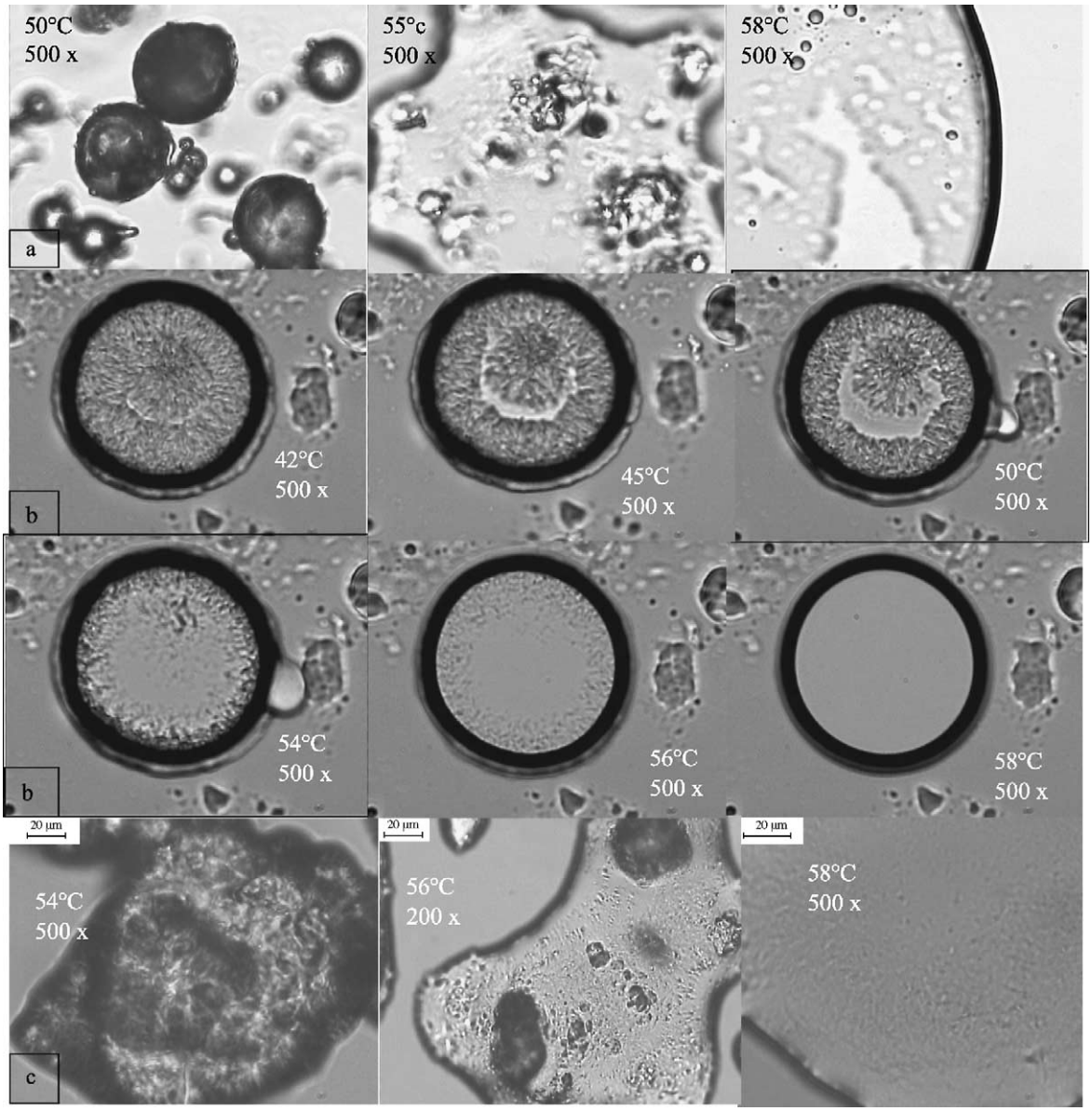

Fig. 6. HSM microphotographs of Precirol (magnification: 500× or 200×) obtained from untreated (a), freshly solidified (b) and aged (c) (stored 2 weeks at 40 °C) samples.

Compritol, which melt at a higher temperature value (72 °C).

The DSC results obtained from the same Compritol–Precirol binary mixtures (freshly solidified sample) are presented in Fig. 8. Although the individual melting endotherm of each glyceride base can be depicted on the different thermograms, a slight decrease of the melting endotherm of Compritol can be observed when the proportion of Precirol in the mixtures is increased. The melting range of binary mixtures occurs between ∼45 and 69 °C, and 45 and 64 °C for C–P 8–2 and C–P 4–6, respectively.

These results show that the use of mixtures of fatty binders presenting well distinct melting temperatures

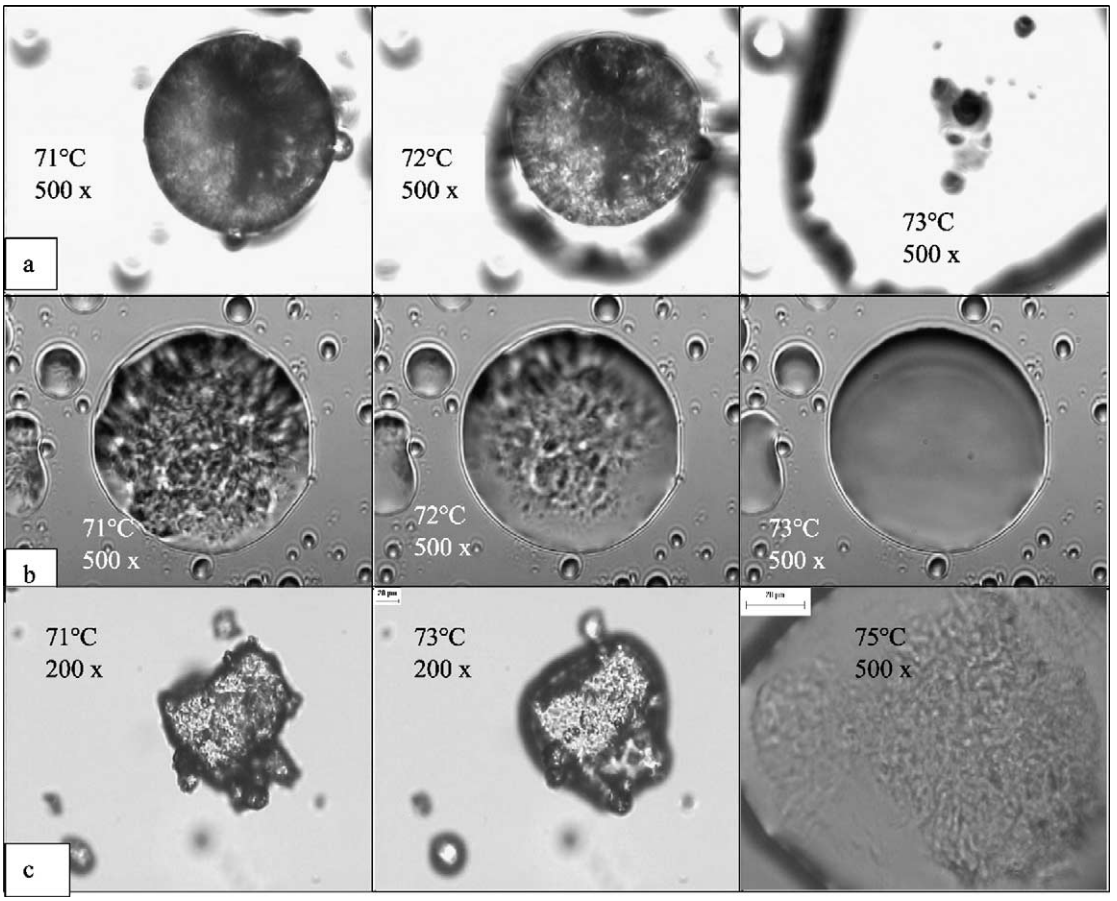

Fig. 7. HSM microphotographs obtained from Compritol (magnification: 500× or 200×) obtained from untreated (a), freshly solidified (b) and aged (c) (stored 5 weeks at 50 °C) samples.

could be a very interesting tool for the preparation of prolonged-release pellets by melt pelletisation, specially when relatively high amounts of lipidic binder have to be used to obtain appropriate drug release properties. As it was largely discussed in a previous paper (Hamdani et al., 2002), the careful control of the product temperature (between 45 and 50 °C) during the pelletisation process permits to control the amount of binder melted, and thus to avoid any "overwetting" phenomenon. DSC and HSM results have shown that

Table 2
The apparent viscosity η_{app} (Pa s) results calculated at a shear rate of 40 s^{-1} for Compritol and Precirol and their binary mixtures, at different temperatures

Meltable excipient	45 °C	50 °C	55 °C	60 °C	65 °C	70 °C	75 °C
Precirol	5196	665	[a]				
Mixture C–P 4–6		965	[a]				
Mixture C–P 6–4		773	302	49.6	[a]		
Mixture C–P 8–2		743	282	127	[a]		
Compritol	–	–	–	5537	1677	19.4	[a]

[a] Melted.

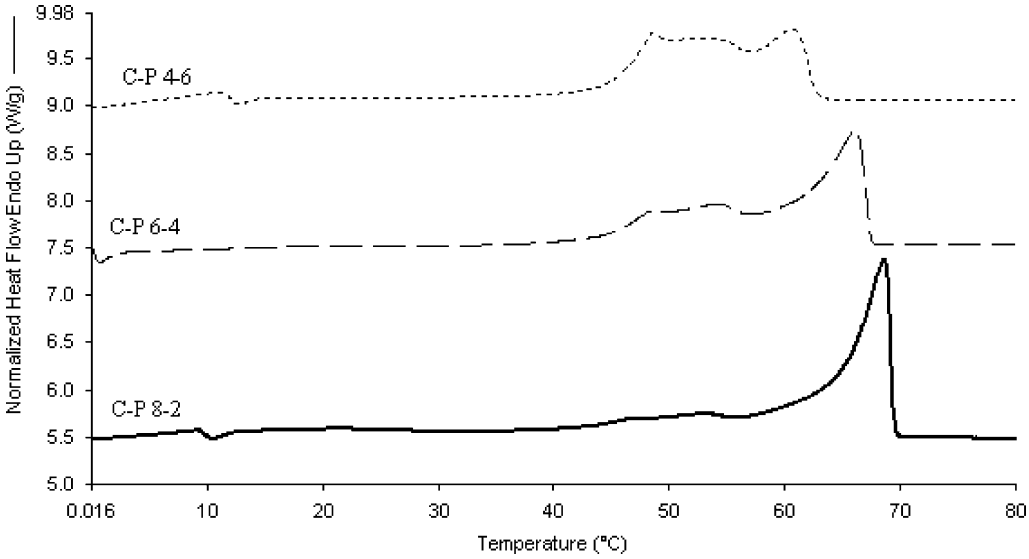

Fig. 8. DSC heating curves of mixtures of Compritol and Precirol (C–P 4–6, C–P 6–4 and C–P 8–2) obtained from freshly solidified samples.

Precirol samples present relatively complex melting behaviour as they melt over a relatively wide range of temperatures, from temperature values as low as ~45–58 °C. Moreover, results obtained by the rheological studies from the unmelted materials show that viscosity values obtained at 50 °C for the different lipidic mixtures are probably sufficiently low (sufficiently softened material) to promote the binder deformation under the action of the high shearing forces developed during melt pelletisation. It's probably the reason why this critical temperature value of 50 °C should not be exceeded when such formulations based on the use of appropriate mixtures of Precirol and Compritol, respectively, as lower and higher melting range fatty binders are considered (Hamdani et al., 2002).

The melt pelletisation technique in high shear mixers might be an advantageous method to produce effective controlled-release pellets in a one-step single-pot production process, as seen in a previous work (Hamdani et al., 2002). However, one limiting factor of this technique is the appropriate temperature control during the process. Consequently, the knowledge of thermal and rheological characteristics of starting materials is necessary before developing such glycerides dosage forms. As the lipidic excipients act as binders, their melting range have to be closely correlated with the product temperature during melt pelletisation process in order to obtain an effective pelletisation while avoiding any "overwetting" phenomenon. Moreover, rheological comportment of fatty binders gives an interesting illustration about the viscosity and the deformation of melting binders under high shear forces in high shear mixers.

4. Conclusion

Compritol and Precirol are very interesting materials which may present potential applications as lipidic binders in melt pelletisation process to develop prolonged-release dosage forms. This study has therefore highlighted the importance of considering the physical, thermal and rheological characteristics of glyceride bases in order to better control the properties of controlled-release formulations. Due to their chemical and physical complexity, the lipophilic binders may exhibit a relatively complex behaviour, i.e. melting and crystallisation, polymorphism, physical modifications.

Both untreated and fresh solidified Precirol and Compritol samples present partially amorphous layered structure which gradually crystallise in time. The rate of crystallisation was found to be more rapid for Precirol, and is highly dependent on the ageing

conditions (storage temperature). The influence of these physical ageing modifications on the drug release properties of glyceride-based prolonged-release dosage forms will be discussed in a future paper.

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