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Effect of aging on the release of salbutamol sulfate from lipid matrices

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Abstract

The aim of the present work was to evaluate the influence of aging that might condition the release of salbutamol sulfate from oral formulations (lipid matrices) using Gelucire® as lipid excipients. Gelucires are essentially characterized by their melting point and their hydrophilic–lipophilic balance. The release profiles of salbutamol sulfate from the capsules elaborated were dependent on the type of Gelucires, fast release, in the case of Gelucire® 35/10, a slower release for Gelucire® 48/09 and a slow release for Gelucire® 46/07. Differential scanning calorimetry was used to study the physical state of drugs in the matrices. Gelucires may exhibit aging effects, whereby a range of physical properties may change upon storage. In the case of Gelucire® 35/10, which presents a fast release of salbutamol sulfate, storage produces a decrease in the values of dissolution constant for all capsule sizes. Gelucire® 48/09 showed a slower release rate than Gelucire® 35/10, and after 1 year of storage, a decrease in the salbutamol dissolution rate for capsule number 3 and 4 was observed. Gelucire® 46/07 presented the slowest dissolution rate, but there were not statistically significant differences. These results show that the faster the dissolution rate, and the larger the capsule size, the higher is the influence of storage.

Keywords: Aging; Sustained release; Salbutamol; Gelucire®

1. Introduction

Many controlled-release dosage forms are designed to release a drug at a predetermined rate, thus maintaining relatively constant drug levels in plasma for an extended period of time. Some benefits may result from the use of these formulations, such as lowering adverse effects, reducing the frequency of dosage and improving patient compliance (Saleh et al., 1993). The use of this type of formulations is convenient particularly for those drugs that have a relatively short elimination half-life and narrow therapeutic index, as is the case of salbutamol (Silver et al., 1988).

Salbutamol is a β-adrenergic receptor agonist, which is used as a bronchodilator in the treatment of reversible bronchospasm. Since the half-life of orally administered salbutamol is approximately 5

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h (Gongora et al., 1991), the drug must be dosed three to four times daily to maintain bronchodilation, thus becoming a possible candidate for the development of controlled or sustained release formulations (Hernández et al., 1996, 1997).

Gelucires excipients are saturated polyglycolized glycerides. Recent studies have reported the use of these Gelucires as excipients to prepare sustained release lipid matrices (Vila-Jato and Delgado, 1990; Brossard et al., 1994). Gelucires are identified by their melting point (ranging from 33 to 65°C) and hydrophilic–lipophilic balance (HLB) (ranging from 1 to 14). Gelucires with low HLB can be employed to decrease the dissolution rate of drugs (Huet de Barochez et al., 1989; Vila-Jato et al., 1990; Vila-Jato and Delgado, 1990), and high HLB ones for fast release (Serajuddin et al., 1988; Smith et al., 1990). Some authors have indicated that the physical instability of the solid dispersions elaborated with Gelucires are due to changes in the melting properties of Gelucires that produces a change in the dissolution of incorporated drugs (Moricout et al., 1990; Sutananta et al., 1993).

The aim of the present work was to evaluate the influence of storage on the release of salbutamol sulfate from formulations using Gelucire® 35/10, 48/09 and 46/07 as lipid excipients. Three capsule sizes were evaluated corresponding to number 1, 3 and 4.

2. Materials and methods

Salbutamol sulfate (USP 23) was supplied by Vencaser S.A. (Bilbao, Spain). 1.2 mg of salbutamol sulfate is equivalent to 1 mg of salbutamol. Gelucire® 35/10, 48/09 and 46/07 were supplied by Gattefossé España (Madrid, Spain). All other chemicals were of analytical grade.

2.1. Formulations

Hard gelatin capsules (number 1, 3 and 4) were filled with salbutamol sulfate and different Gelucire® 35/10, 48/09 and 46/07. Gelucire was melted in a thermostatic bath at a temperature 10°C above its melting point. The active substance was incorporated by stirring until a dispersion was obtained. Afterwards, the capsules were filled with the mixture and cooled. Once prepared, the capsules were stored for 1 year at room temperature.

2.2. DSC

Gelucires containing 50% w/w concentration of salbutamol sulfate were subjected to calorimetric characterization. Samples were examined before and after 1 year storage by differential scanning calorimetry (DSC). Differential scanning calorimetry (DSC) thermograms were obtained by employing a DSC-50 Shimadzu instrument. A heating rate of 5°C min^{-1} was used from 10 to 220°C in nitrogen atmosphere. Samples were prepared for DSC studies by weighing accurately 7 mg into an aluminum DSC pan which was then covered and crimped. Indium standard was used for calibration.

2.3. Dissolution test

Dissolution tests (six replicates, one capsule per vessel) were performed using a USP 23 type II apparatus (The United States Pharmacopeia 23, 1995) in deionized water (1000 ml), at 100 rpm and 37 ± 0.5°C. Samples of 5 ml were withdrawn at fixed time intervals, filtered through a 0.45-μm filter (Millipore) and replaced with the same volume of dissolution medium. The dilution caused by this addition was corrected when the amount of drug released into the medium was calculated. The dissolved amount of drug, at each time was expressed as a percentage of the dose.

The concentration of salbutamol was determined by a spectrofluorimetric method using a KONTRON SFM 25 apparatus at the 220 nm (excitation) and 309 nm (emission) wavelengths. Gelucires excipients were tested for fluorescence emission at these wavelengths, and no interference with salbutamol determination was experienced. The relationships between fluorescence and concentration of salbutamol was found to be linear between 0.1 and 10 μg ml^{-1}, with correlation coefficients above 0.999, and the sensitivity was constant in the range of concentrations. The results obtained in the repeatability assay were ex-

pressed as coefficients of variation and the top value was 2.03%; for the reproducibility, the highest value was 2.71%. The limit of quantification was 0.1 μg ml^{-1}.

2.4. Data analysis

The influence of Gelucire characteristics on the release of salbutamol was evaluated in terms of the parameters calculated by non-linear equation Eq. (1) (Peppas, 1985),

$$\frac{M_t}{M_\infty} = Kt^n \quad (1)$$

where M_t/M_∞ is the fraction of drug release up to time t; K is a constant incorporating the structural and geometric characteristics of the release device, and n is the release exponent indicative of the release mechanism.

The curves were fitted with WinNonlin (WinNonlin, 1995), a non-linear regression analysis program. The program is based on the Nelder–Mead algorithm and run on a PC. The goodness of fit was evaluated on the basis of the weighted squared residuals Akaike's information criterion values, R^2, and the correlation coefficient (Wagner, 1993).

Mean dissolution time (MDT) is the mean ratio of the first to zero moments of the dissolution rate–time curve and it is expressed by the following Eq. (2) (Brockmeier and Von Hattinberg, 1982),

$$\mathrm{MDT} = \frac{\mathrm{ACC}}{M_\infty} \quad (2)$$

where ACC is the area complementary to the area under the accumulated dissolution curve and M_∞ is the accumulated amount dissolved at maximum time. This parameter was calculated by the PKCALC program (Schumaker, 1986).

The statistic analysis was performed by using the Stat View™ + Graphics program, (1988) and the Student t-test and the ANOVA (one and two way) were chosen.

3. Results

Fig. 1 shows the dissolution profiles of salbutamol sulfate from the three different capsule sizes elaborated with the three types of Gelucires at time zero and after storage at room temperature for one year. Significant changes in the dissolution profiles of the active principle can be observed depending on storage time. For Gelucire® 35/10 and for the three capsule sizes studies, a decrease in the release rate of the active principle takes place during storage. In Gelucire® 48/09 capsule size also influences the biopharmaceutic stability of the formulation.

For capsule size numbers 3 and 4, a delay in the release rate of salbutamol sulfate is observed depending on storage. However, storage after one year at room temperature does not cause any change in the dissolution profiles for the same Gelucire and capsule size number 1. Lastly, for Gelucire® 46/07 storage does not cause any change in the dissolution profiles no matter what the capsule size is.

Table 1 shows the kinetic parameters obtained for Gelucire® 35/10 from the non-linear equation. For this Gelucire, the storage produced a decrease in dissolution constant values for all capsule sizes. The percentage of reduction for capsule number 1 is 47.01%. This percentage is 44.05 and 64.21% for capsule number 3 and 4, respectively. In addition to the modifications in the dissolution constant, there is an increase in the values of the mean dissolution time for the different capsule sizes, 307.41% for capsule number 1; 282.75% for number 3 and 577.26% for number 4. These differences were statistically significant in all cases ($P < 0.05$).

Table 2 shows the kinetic parameters obtained for Gelucire® 48/09. This Gelucire showed a slower release rate than Gelucire® 35/10. The most important changes due to storage are found in the rate constant of number 4 capsules; their value ranged from $2.10 \pm 0.18\%$ min^{-n} ($t = 0$) to $1.35 \pm 0.02\%$ min^{-n} ($t = 1$ year) and the MDT values increased 121.40%. These decreases in the parametric values were statistically significant ($P < 0.05$) for number 3 and 4 capsules; however, no statistical differences ($P > 0.05$) were observed for the kinetic parameters for number 1 capsules.

Gelucire® 46/07 showed the slowest dissolution rate. The release mechanism of salbutamol sulfate from this Gelucire could be explained by an ero-

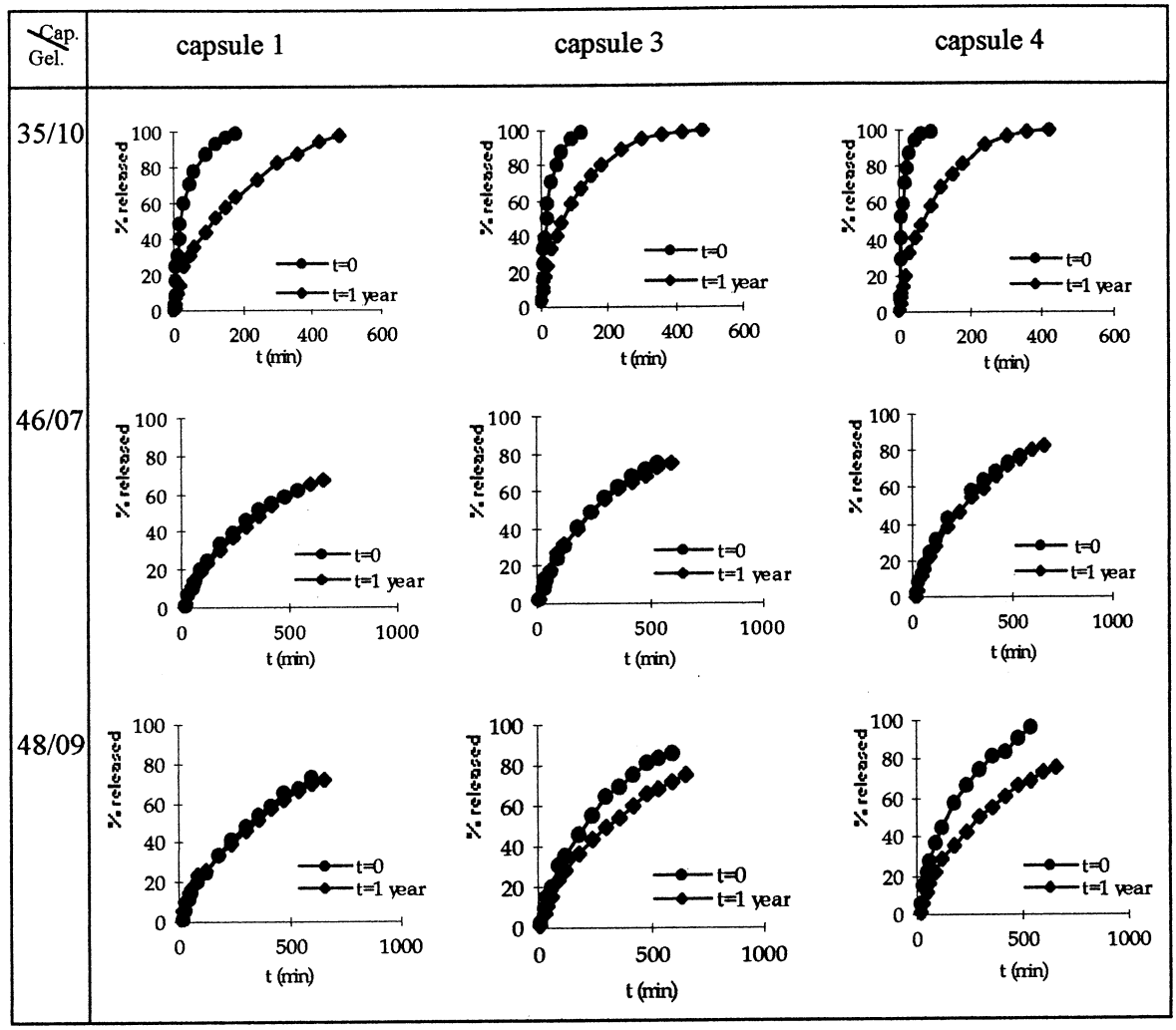

Fig. 1. Influence of storage on salbutamol sulfate release from lipid matrices.

Table 1
Kinetic parameters and MDT of salbutamol sulfate release from Gelucire® 35/10 matrices

Gelucire® 35/10						
Cap.	K (% min^{-n})		n		MDT (min)	
	$t=0$	$t=1$ year	$t=0$	$t=1$ year	$t=0$	$t=1$ year
1	7.53 ± 2.28	3.99 ± 0.77	0.60 ± 0.05	0.53 ± 0.03	38.44 ± 10.37	156.61 ± 14.67[a]
3	7.99 ± 2.64	4.47 ± 1.26	0.66 ± 0.06	0.53 ± 0.11	26.55 ± 10.26	101.62 ± 29.95[a]
4	12.60 ± 2.45	4.51 ± 1.24	0.72 ± 0.14	0.57 ± 0.05	14.14 ± 2.04	95.77 ± 17.33[a]

[a] Statistically significant ($P<0.05$).

Table 2
Kinetic parameters and MDT of salbutamol release from Gelucire® 48/09 matrices

Gelucire® 48/09						
Cap.	K (% min^{-n})		n		MDT (min)	
	$t=0$	$t=1$ year	$t=0$	$t=1$ year	$t=0$	$t=1$ year
1	0.89 ± 0.31	0.98 ± 0.31	0.70 ± 0.04	0.69 ± 0.05	447.47 ± 19.38	465.73 ± 17.16
3	1.41 ± 0.41	1.17 ± 0.09	0.67 ± 0.06	0.65 ± 0.02	315.01 ± 28.10	436.85 ± 18.14[a]
4	2.10 ± 0.18	1.35 ± 0.02	0.63 ± 0.01	0.59 ± 0.02	195.41 ± 2.94	432.63 ± 20.71[a]

[a] Statistically significant ($P<0.05$).

Table 3
Kinetic parameters and MDT of salbutamol release from Gelucire® 46/07 matrices

GELUCIRE® 46/07						
Cap.	K (% min^{-n})		n		MDT (min)	
	$t=0$	$t=1$ year	$t=0$	$t=1$ year	$t=0$	$t=1$ year
1	0.99 ± 0.17	0.97 ± 0.44	0.66 ± 0.02	0.65 ± 0.04	460.35 ± 16.24	466.86 ± 10.03
3	1.24 ± 0.29	1.23 ± 0.62	0.66 ± 0.04	0.61 ± 0.02	391.58 ± 19.35	404.28 ± 6.92
4	1.21 ± 0.25	1.06 ± 0.18	0.67 ± 0.03	0.68 ± 0.02	376.65 ± 21.97	380.76 ± 14.31

Table 4
Values of n index obtained after fitting the release profile to the non linear equation

Cap.	Gelucire® 35/10		Gelucire® 48/09		Gelucire® 46/07	
	$t=0$	$t=1$ year	$t=0$	$t=1$ year	$t=0$	$t=1$ year
1	0.60 ± 0.05	0.53 ± 0.03	0.70 ± 0.04	0.69 ± 0.05	0.66 ± 0.02	0.65 ± 0.04
3	0.66 ± 0.06	0.53 ± 0.11	0.67 ± 0.06	0.65 ± 0.02	0.66 ± 0.04	0.61 ± 0.02
4	0.72 ± 0.14	0.72 ± 0.05	0.63 ± 0.01	0.59 ± 0.02	0.67 ± 0.03	0.68 ± 0.02

sion of the inert mass of the Gelucire (Vial-Bernasconi et al., 1995). Table 3 shows the kinetic parameters obtained. No statistically significant differences ($P > 0.05$) were found in the kinetic parameters studied (K and MDT). We could, therefore, conclude that in this slow-rate Gelucire, one-year storage does not cause changes in the release profiles and its biopharmaceutical stability is maintained during this period of time.

The influence of aging on the release mechanism of the drug from the matrix system using values of n index obtained after fitting the release profile to the non-linear equation is shown in Table 4. Once the statistical analysis was carried out, it was found that storage time does not change the value of n index significantly ($P > 0.05$) for any of the capsule sizes of the different Gelucires studied. Therefore, we could conclude that the release mechanism of salbutamol sulfate is maintained during the storage time studied (1 year).

In order to analyze the possible influence of aging on salbutamol sulfate and the Gelucire in the formulations, we carried out studies of differential scanning calorimetry (DSC) of the melted mixtures of the Gelucires used in the preparation

of the lipid matrices (42/12, 46/07 and 48/09) with the drug (salbutamol sulfate) with a 50:50 proportion and at $t = 0$ and 1 year. Figs. 2–4 show the different results. These materials, like all glyceride-based products, melt over a range of temperature, hence the interpretation of the thermal data is often difficult. The thermograms show an endotherm close to 200°C, which refers to the fusion with degradation of the active principle. None of the three mixtures studied shows important variations in their calorimetric behavior depending on storage time ($t = 0$ and 1 year).

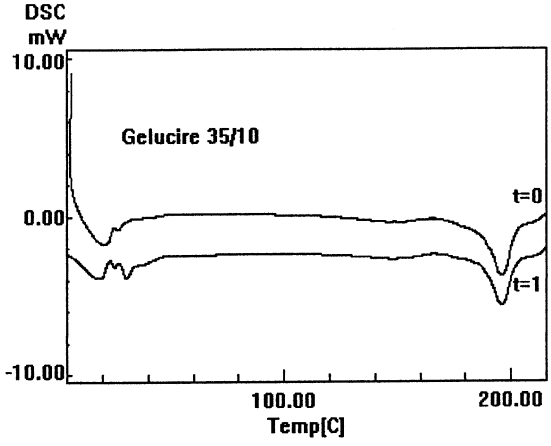

Fig. 2. DSC curves of Gelucire® 35/10 ($t = 0$ and 1 year).

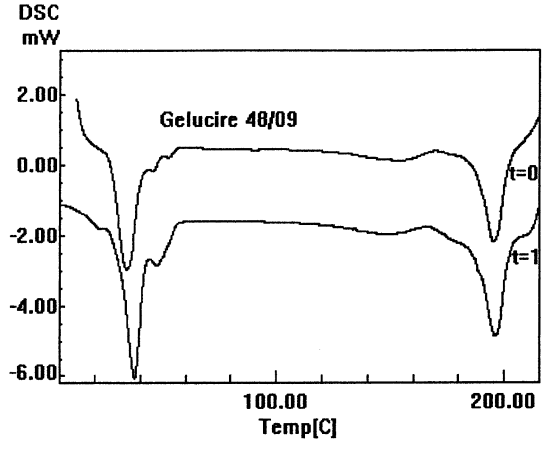

Fig. 3. DSC curves of Gelucire® 48/09 ($t = 0$ and 1 year).

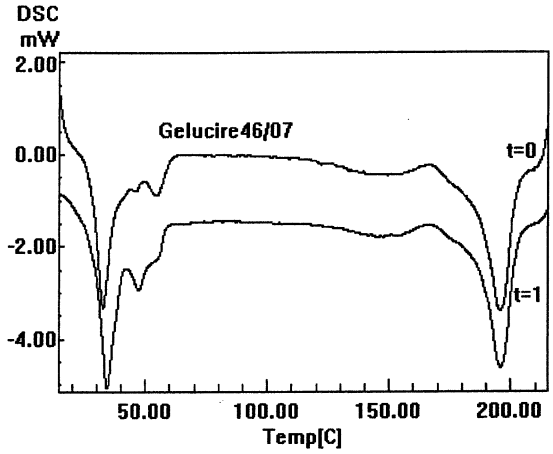

Fig. 4. DSC curves of Gelucire® 46/07 ($t = 0$ and 1 year).

4. Discussion

It is well established that glyceride-based products may exhibit aging effects, whereby a range of physical properties may change on storage of the bases which are sometimes accompanied by changes in the in vitro and in vivo release of drug from the dosage form. The mechanism responsible for these changes has been attributed to either the conversion of triglycerides to more stable polymorphic forms (Liversidge et al., 1981) or the conversion from the amorphous to the crystalline state of the bases (Coben and Lordi, 1980; Laine et al., 1988). Several studies have examined the drug release properties of the Gelucires bases with many investigations attempting to relate the physical and chemical properties of the Gelucires to the dissolution rate (Howard and Gould, 1987; Bodmeier et al., 1990; Kopcha et al., 1990; Prapaitrakul et al., 1991; Sutananta et al., 1994, 1995; Esquisabel et al., 1996).

The Gelucires with a fast release of salbutamol sulfate show a high degree of deformation or disintegration after 1 h in simulated gastric juice at 37°C, with a mass that either spreads on the surface or softens. This fast release could be due to a fast solubilization and disintegration of the Gelucire 35/10 in the dissolution media eased by their low melting point (Doelker et al., 1986). Several authors (Bernasconi et al., 1985; Doelker et al., 1986) found that Gelucire 48/09 exhibits an

inert mass which remains intact but softens after 1 h in simulated gastric juice. The release mechanism from this Gelucire may be due to a hydration with gelation and the subsequent diffusion of the drug from the resultant mass (Kopcha et al., 1990). Gelucire 46/07 had slower dissolution rate. This Gelucire is characterized by high melting points and low hydrophilic–lipophilic balance values. Gelucire 46/07 is an inert mass in an aqueous medium, but in simulated gastric juice at 37°C and after 1 h it takes the form of an entire mass which floats in the medium (Ratsimbazafy and Brossard, 1991). The release mechanism from this Gelucire could be explained by an erosion process.

Previous studies carried out in our laboratory had indicated that when increasing capsule size, a retardation of the release process of salbutamol sulfate from formulations using Gelucire as lipid excipients, takes place (San Vicente et al., 1999). Similar results have been obtained by other authors with different drugs (Doelker and Buri, 1981; Mc Taggart et al., 1984) concluding that this is due to a decrease on the contact surface between the drug and the dissolution medium. In this work, we have studied how capsule size affects drug release during storage process. The higher the capsule size, the higher is the storage effect on the release process. These changes are significant for the Gelucire® 35/10 and 48/09. The changes observed in the release profiles of salbutamol sulfate depending on size can be related to the relative percentage of drug and Gelucire. The larger the capsule size, the larger is the percentage of excipient that can change affecting drug release. Moreover, Gelucires with the lowest melting point show the most significant effect since these Gelucires may undergo the largest changes during storage.

The changes observed in the release rate of salbutamol sulfate from our lipid matrices may be due to modifications both in the active principle and in the excipient, although, in our case, the percentage of active principle active was much lower than the one used in studies carried out with other drugs. Bodmeier et al. (1990) claim that, if the amount of drug dissolved in wax during the melting process exceeds, the solubility of the drug in the matrix at storage temperature, the drug may crystallize over time and cause stability problems. On the other hand, according to Moricout et al. (1990), when the active principle appears in different alotropic forms and is dissolved in the excipient, it can turn into more stable ones inside the Gelucire. In a study by Huet de Barochez et al. (1989), in which capsules with Gelucire® 50/02 and 62/05 were stored at 25, 37 and 50°C, a faster dissolution of a very hydrosoluble active principle ($pK = 4–9$) was observed for all the formulations after three months of storage. The authors explain this as a result of polymorphism and a partial fusion of Gelucire during storage of the formulations. However, there are no studies that refer to the presence of polymorfs in the case of salbutamol. Ward and Schultz (1995) have studied the effect of sorbed water and the physical properties of both micronized and unmicronized salbutamol. Amorphous to crystalline conversions are observed, the kinetics of which are found to be both temperature and relative-humidity dependent.

Another possibility is that structural changes in the Gelucires take place during storage (Doelker et al. 1986). Excipients containing fat products can react spontaneously with oxygen (Naudet, 1963). This auto-oxidation process is more important when the degree of insaturation of the material and the temperature increase. Lipid excipients made up of triglycerides can undergo polymorphic transitions, precipitations and crystallizations with the passage of time which is followed by changes in their properties and in the release rate of the active principle. In our study, the fast-release dosage forms show the greatest alterations. These results could be due to the low melting point of the Gelucire. For Gelucire 35/10, fairly large percentage may be liquid at the storage temperature which could then recrystalize on storage (Laine et al., 1988).

5. Conclusions

Aging can cause alterations in the biopharmaceutic parameters of salbutamol sulfate capsules, alterations that depend on the type of Gelucire

and the size of capsule used. The most significant changes can be observed in Gelucire® 35/10, whereas storage does not have any influence on the release of salbutamol sulfate in Gelucire® 46/07. Regarding the influence of capsule size, this study has shown that when increasing capsule size, the changes of the release profiles of salbutamol sulfate obtained were found to be more important. These results show that the influence of aging on the release of the active principle is more important in the fast release Gelucire and large capsule size than in the slow release and small capsule ones.

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