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Dissolution stability of multiparticulate controlled release tablets

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Abstract

Dissolution stability is evaluated on three multiparticulate membrane controlled release tablet formulations. The evaluation is based on analysis of the parameters in the Order Model that is used to characterize the dissolution profiles. By a simple statistical–graphical approach, the change during storage is evaluated, and mechanisms likely to be responsible for instability are identified. The method is more sensitive than the classical evaluation of dissolution data in fixed points. A high-stress condition (50°C/ambient humidity in 10–21 days) was used to make the tablets unable to disintegrate. Dissolution profiles from these tablets were fitted to the Order Model thus showing how the parameters are affected by slow and incomplete disintegration. This knowledge facilitated interpretation of 40°C storage data as the observed effects could be differentiated into disintegration-related and release mechanism-related. For the three tested products, the stability analysis showed that the disintegration properties play a predominant role for the dissolution stability. © 1997 Elsevier Science B.V.

Keywords: Dissolution; Stability; Multiparticulate; Diffusion membrane; Order model; Tablet disintegration

1. Introduction

The dissolution of a controlled release tablet is one key property of the product. Equally important is the stability of dissolution during the storage. The industry uses many resources to investigate dissolution stability of a controlled release product. However, not much research has been directed toward this area.

For multiparticulate tablets, the dissolution profile is controlled by the dissolution properties of the individual units and by the disintegration ability of the tablet. Thus, dissolution instability might be due to both aspects.

Murthy and Ghebre Sellassie (1993) reviewed dissolution stability and concluded that dissolu-

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tion stability trials are mainly useful for the technical quality control.

Dissolution stability is usually evaluated on release data sampled at the fixed time points given in the product specifications (e.g. 1, 2 and 6 h). Such results are suitable for final formulations to ensure the quality, but do not give much information about the reasons for possible changes in the dissolution rate. For that purpose, characterization of the dissolution profiles by a mathematical expression is advantageous—provided sufficient data are sampled to ensure accurate parameter estimates.

Rubino et al. (1985) used the Weibull function to fit their release profiles and used ANOVA on the parameters of the function to evaluate drug excipient interactions. They found this approach very useful to obtain specific formulation-related information. However, as regards the statistical method, they apparently did not take into account that time-randomization is not possible in a stability trial. To overcome that problem and still combine the analysis of storage time with other factors (e.g. temperature, humidity, packaging, batch etc.), Langenbucher (1991) suggests usage of analysis of covariance in a general linear model (GLM). For the present study, however, the assumed linearity of the storage effects is inexpedient as the progress of possible changes are also in focus (the statistical approach used is described in the subsequent paragraph).

The Weibull function provides excellent fitting ability but according to our experience the shape parameter and the lag-time parameter may be confounded. Minimization of that risk is one of the advantages attained by using the Order Model (Jørgensen and Christensen, 1996) for the profile fitting. Contrary to the shape parameter in the Weibull function, the shape parameter in the Order Model (the kinetic order) is not influenced by the initial part of the profile.

Prediction of chemical stability based on kinetic degradation studies using various conditions (temperature, humidity, pH and buffer capacity) has long been used. Different techniques including the Arrhenius plotting are discussed by Carstensen et al. (1992) and they state that a similar technique is not available for dissolution stability. Dukes (1984) also points that mathematical modelling of dissolution stability has limited relevance as storage-induced changes in dissolution behaviour usually appear to be unpredictable.

The aim of this paper is:

- to illustrate how storage-induced dissolution changes may be characterized by the Order Model
- to demonstrate a systematical approach for interpretation of parameter changes in relation to multiparticulate controlled release formulations
- to discuss the predictability of dissolution stability—in particularly in relation to data obtained from accelerated storage conditions.

2. Materials and methods

2.1. Formulations

Three multiparticulate membrane controlled release tablet formulations were tested. Two of them contained coated ibuprofen cores produced by extrusion and spheronization and subsequent coating. The two core compositions are described in Jørgensen (1996) as the 'PVP-core' and the 'CMC-core' referring to the binders being Polyvidon-type VA 64 and sodium carboxy methyl cellulose, respectively. Except for the binders the two formulations are similar. In this paper, the two formulations are designated as 'IBU-PVP' and 'IBU-CMC'. The third formulation, 'ASA' contained coated acetyl salicylic acid crystals and had composition similar to Acetard®.

The coating used for all three formulations was ethyl cellulose-based diffusion coating. The tablet composition was also similar for the three formulations.

2.2. Dissolution methods

The dissolution tests of IBU-CMC and IBU-PVP tablets were conducted in a Sotax AT 7 dissolution apparatus using rotating baskets (USP/Ph.Eur, method 1), 100 rpm, 37°C and 900 ml pH 7.2 phosphate buffer. The dissolution tests of ASA tablets were conducted in a Sotax AT 7

dissolution apparatus using paddles (USP/Ph.Eur, method 2), 75 rpm, 37°C and 900 ml 0.1 N hydrochloric acid. In all experiments, the dissolution medium was degassed before the test by vacuum filtration through a glass fiber filter, Whatman GF/A. The sampling and spectrophotometrical measurement (221.8 nm for ibuprofen and 232 nm for ASA, 0.1 cm cuvettes) was performed in an automatic dissolution system (Lambda 2 and 'PEDS' version 2.1 and 3.0 from Perkin Elmer).

Each of the dissolution tests was run until all the drug substance was released (20–50 h) during which period between 80 and 200 data points were collected for the dissolution profile.

2.3. Stability design

The three tablet formulations were stored at 25°C/60% RH (25/60) in closed containers, at 40°C/ambient humidity (40/amb) in closed containers and 40°C/75% RH (40/75) in open containers and tested each 1 1/2 months. The accuracies of the temperatures were ± 2°C and for the humidities ± 5% RH. Besides, 'high-stress' experiments were carried out in which the tablets were stored at approximately 50°C and ambient humidity (50/amb) in 10–21 days in open Petri jars.

2.4. Fitting the parameters of the Order Model

The dissolution profiles were parametrically characterized by the 'Order Model' (Jørgensen and Christensen, 1996), which can be written as

$$m(t) = m(\infty)[1 - (1 - (1 - n)k(t - f(t_0)))^{1/1-n}] \quad (1)$$

where $m(t)$ is the amount of dissolved drug at time, t, $m(\infty)$ is the total amount of drug (i.e. the assay), n is the release kinetic order and k is the rate constant. The term, $f(t_0)$, is a lag-time function, given by

$$f(t_0) = t_0[1 - \exp(-t/abs(t_0))] \quad (2)$$

In Eq. (2) the lag-time, t_0, is affected gradually as illustrated in Jørgensen and Christensen (1996). The four parameters of the order function were estimated using non linear regression in Statgrafics 6.0 (minimizing the sum of squares using a Marquardt search procedure).

2.5. Interpretation of parameter changes

Evaluation of dissolution stability was systematized by analysis of t_0, k and n of the Order Model. Any storage effect thus becomes one of 27 ($=3^3$) possible events as each of the three parameters either remains constant, increases or decreases. Table 1 contains the six single parameter changes and thus any storage effect is indicated by one of these or by combination of two or three of them.

In Table 1, the effects on mean dissolution time (MDT) of changes in the three parameters are stated. MDT expresses the overall degree of retardation and was calculated by the following expression:

$$\mathrm{MDT} = t_0 + \frac{1}{k}\frac{1}{2-n} \quad (3)$$

The quantitative changes in t_0, k and n do not show directly the changes in MDT. The ΔMDT may be expressed as a function of Δt_0, Δk and Δn as:

$$\begin{aligned}\Delta\mathrm{MDT} &= \mathrm{MDT}_2 - \mathrm{MDT}_1 \\ &\approx \Delta t_0 - \frac{\Delta k}{k_1 k_2\sqrt{(2-n_1)(2-n_2)}} \\ &\quad + \frac{\Delta n}{\sqrt{k_1 k_2}(2-n_1)(2-n_2)}\end{aligned} \quad (4)$$

here subscripts '1' and '2' denote before and after storage, respectively.

As concomitant changes in t_0, k and n may not reflect in ΔMDT another term, the total change of dissolution (TCD) was defined. TCD is given by:

$$\begin{aligned}\mathrm{TCD} &= |\Delta t_0| + \frac{|\Delta k|}{k_1 k_2\sqrt{(2-n_1)(2-n_2)}} \\ &\quad + \frac{|\Delta n|}{\sqrt{k_1 k_2}(2-n_1)(2-n_2)}\end{aligned} \quad (5)$$

The storage effect on t_0, k and n is by this method translated to 'MDT-units' (i.e. the unit of time, hours or minutes) and the difference be-

Table 1
Characteristics and explanations for single parameter storage induced changes of t_0, k and n in the Order Model

Parameter change	MDT effect	Characteristics and possible explanations related to storage of multiparticulate tablets
None	None	Stable
t_0 ↑	↑	Characteristics: initial slower dissolution. Explanations: slower disintegration; less permeable membranes (reduced free volume); occurrance of a new release mechanism during dissolution test.
t_0 ↓	↓	Characteristics: initial faster dissolution. Explanations: migrated drug to the tablet surface; membrane damage; formation of pores in the membranes (e.g. by plastiziser phase separation).
k ↑	↓	Characteristics: faster dissolution for $t > t_0$. Explanations: membrane damage; formation of pores (e.g. by plastiziser phase separation).
k ↓	↑	Characteristics: slower dissolution for $t > t_0$. Explanations: slower disintegration affecting the overall release mechanism; less permeable membranes (reduced free volume); compaction (reduced wettability) of pellet cores.
n ↑	↑	Characteristics: more curved dissolution profile; prolonged termination phase. Explanations: incomplete disintegration of the tablets; increased variation between pellets caused by disintegration of some pellets.
n ↓	↓	Characteristics: less curved dissolution profile; shortened termination phase. Explanations: more homogeneous pellet behaviour, e.g. caused by compaction of the pellet cores (that retards pellets with damaged coating but does not affect the pellets with intact coating). Improved disintegration properties.

↑ and ↓ denote increases and decreases, respectively.

tween ΔMDT (without sign) and TCD expresses the degree of counteracting changes. The TCD and ΔMDT were calculated as percentages relative to the MDT obtained for the start analysis.

2.6. Statistical analysis

A simple combined statistical–graphical method was used to evaluate storage effects. The basis is a calculation of an overall standard error, s_{pool}, in each stability trial obtained by pooling the standard deviations for the included experiments. Thus, homogeneity of the random variance of the experiments is the only assumption required. The number of degree freedoms is $N-r$, where N is the total number of observations and r is the number of experiments. The confidence interval for an experiment with n_i observations is thus given by

$$\text{Conf. interval} = \bar{x}_i \pm \frac{s_{\text{pool}}}{t_{0.975}(N-r)\sqrt{2n_i}} \quad (6)$$

where $\bar{x}_i$ is the average value of the measured quantity in the ith experiment and $t_{0.975}$ refers to the 97.5% fractile of the Student's t-distribution. (The Least Significant Difference model is used. The calculation principle gives intervals that are narrowed (by a factor $\sqrt{2}$) compared with ordinary confidence intervals. The model is suitable for planned pairwise testing—in this case of an observation from the storage period against the values of the start analysis). By plotting these confidence intervals arranged after storage conditions, possible storage effects may be interpreted by the figures.

3. Results and discussion

3.1. Goodness of fit

All dissolution profiles were fitted by the Order Model on the 80–200 data points, and the attained coefficients of determination were between 0.998 and 0.99998 (typically approximately

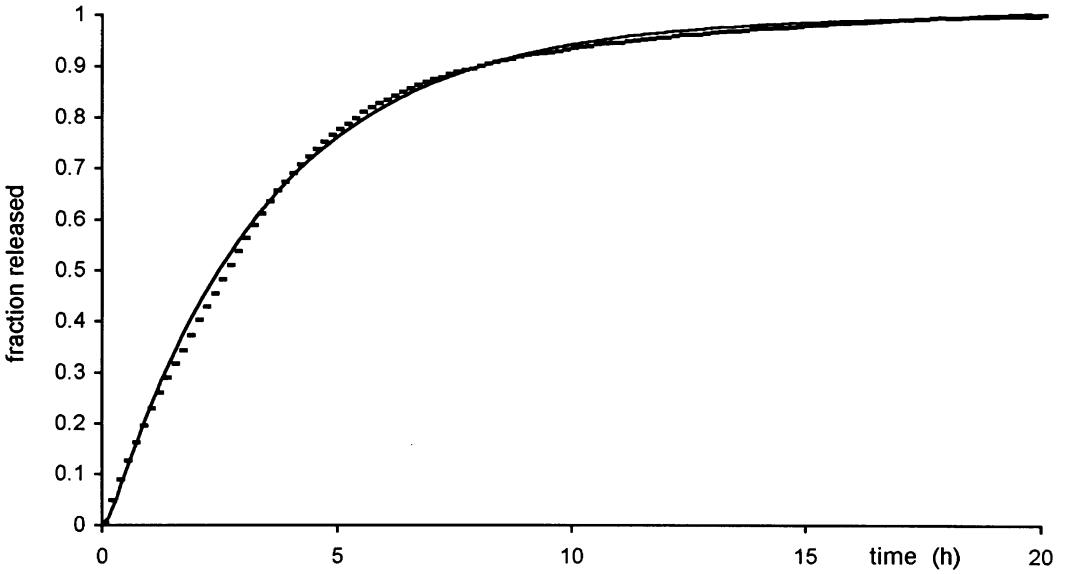

Fig. 1. Goodness of fit illustrated by the poorest data fit (coefficient of determination = 0.998) included in the analysis of parameter changes. The markers are the observed values, and the line is the profile fitted by the Order Model (Eqs. (1) and (2)).

0.9999). Estimation of the $m(\infty)$ by fitting is important to ensure the high precision of the three other parameter estimates. Usage of a theoretical value of $m(\infty)$ will not give equally good parameter estimates. The poorest fit is shown in Fig. 1. The standard error, δ, of the parameter estimates was typically diminutive (poorest fit: $\delta(n) = 0.02$, $\delta(k) = 0.006$ h^{-1} and $\delta(t_0) = 1.5$ min). For the analysis of parameter changes, the contribution from lack-of-fit, therefore, was insignificant.

3.2. The stability trials

To illustrate different aging mechanisms, the evaluation technique is illustrated with stability trials for the three products.

3.3. Multiparticulate IBU-PVP tablets

It appears from Fig. 2 that storage in 10 days at 50/amb (i.e., the 'stress' condition) slows down the dissolution and it was observed that this storage also caused slow and incomplete disintegration. As seen from Fig. 3—and as expected—t_0 and n increased and k decreased. A 6-months storage at 40/75 and 40/amb apparently gives only minor changes. However, as can be seen in Fig. 3, t_0, k and n clearly do change during storage at these conditions. Furthermore, Fig. 3 indicates a time dependency for tablets stored at 40/amb, whereas the levels after 1 1/2 months of storage at 40/75 apparently are almost stable throughout the period. The mechanism involved for the tablets stored at 40/amb is less obvious than for 50/amb storage. Both t_0 and k change in the same directions as in the 'stress' experiment, but the kinetic order is decreased after storage at 40/amb whereas it is increased after the 'stress' storage. Thus, obviously the 40/amb storage induces an effect that is not exclusively explained by the slow and incomplete disintegration. As stated in Table 1, decreased n may be caused by a more homogeneous pellet behaviour due to compaction of the pellet cores. This will slow down the fastest releasing pellets (those with damaged membranes) more than those with intact membranes. This explanation fits the observations very well but other possibilities exist, e.g. an effect of a slightly increased disintegration time (that also retards the fastest pellets most).

As shown in Table 2, the storage at 40/amb and 40/75 increased the MDT. However, as the TCD is higher than the ΔMDT the change of release was higher than indicated by the ΔMDT.

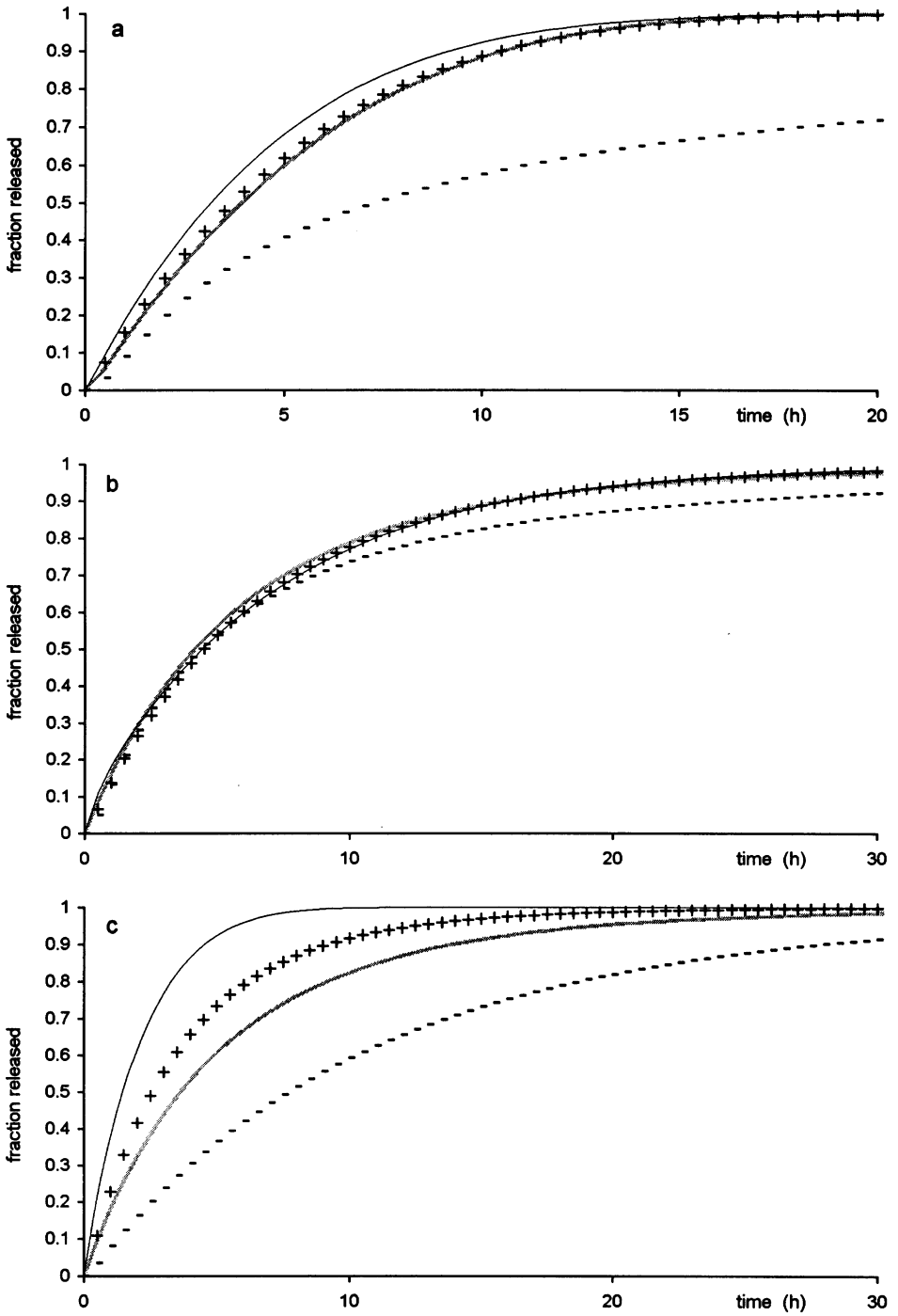

Fig. 2. Dissolution profiles for IBU-PVP tablets (a), IBU-CMC tablets (b) and ASA tablets (c). Fine line: start; heavy gray line: 40/amb; crosses: 40/75; marks: stress (10 days at 50/amb (a and b) and 21 days at 50/amb (c)).

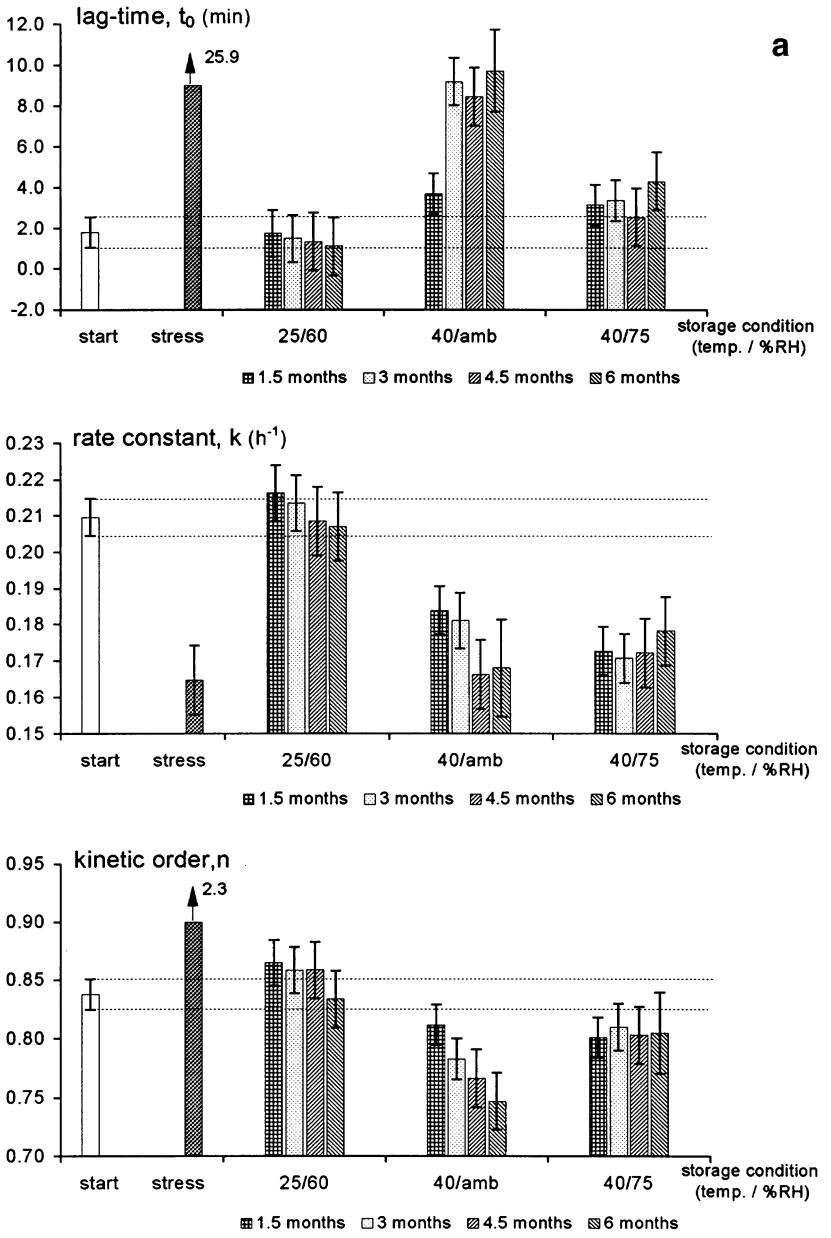

Fig. 3. Stability analysis by means of the three parameters of the Order Model, t_0, k and n for IBU-PVP tablets (a), IBU-CMC tablets (b) and ASA tablets (c). The dotted lines delimit the confidence interval of the start analysis. Confidence intervals of other observations not overlapping the interval of the dotted lines correspond to significant changes. Confidence intervals are calculated by Eq. (6).

3.4. Multiparticulate IBU-CMC tablets

The aging mechanism illustrated by the IBU-CMC tablets is related to the 'aggregation phenomenon' (Jørgensen, 1996) which causes membrane damage on pellets that aggregate during the dissolution test. For some non-disintegrated tablets the aggregation phenomenon was

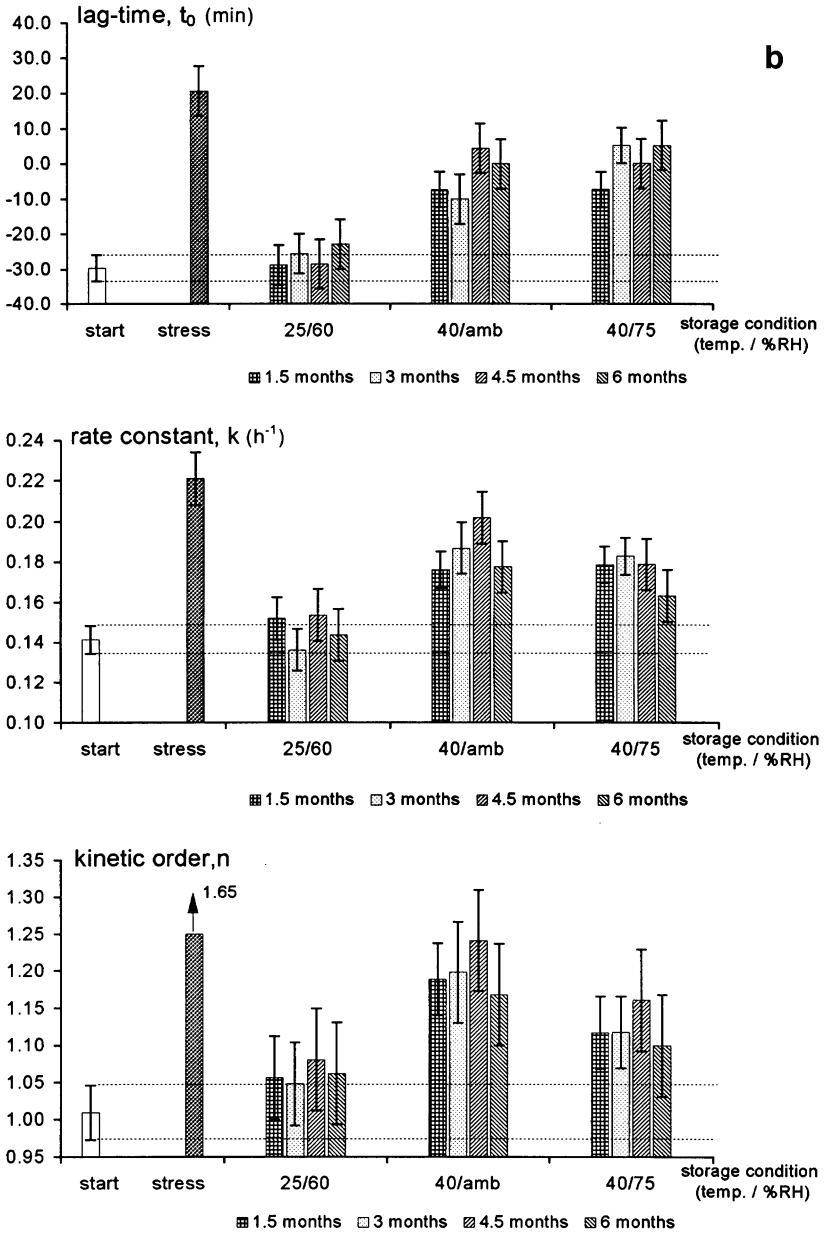

Fig. 3.

also observed. The effects of the aggregation phenomenon on the dissolution were an increased t_0, increased k, increased n and decreased MDT. As appears from Fig. 3b, the changes of t_0, k and n for IBU-CMC tablets follow that pattern. However, the aggregation effect apparently is mixed with other effects as the MDT is unchanged for 25/60, 40/amb and 40/75 and increased for the

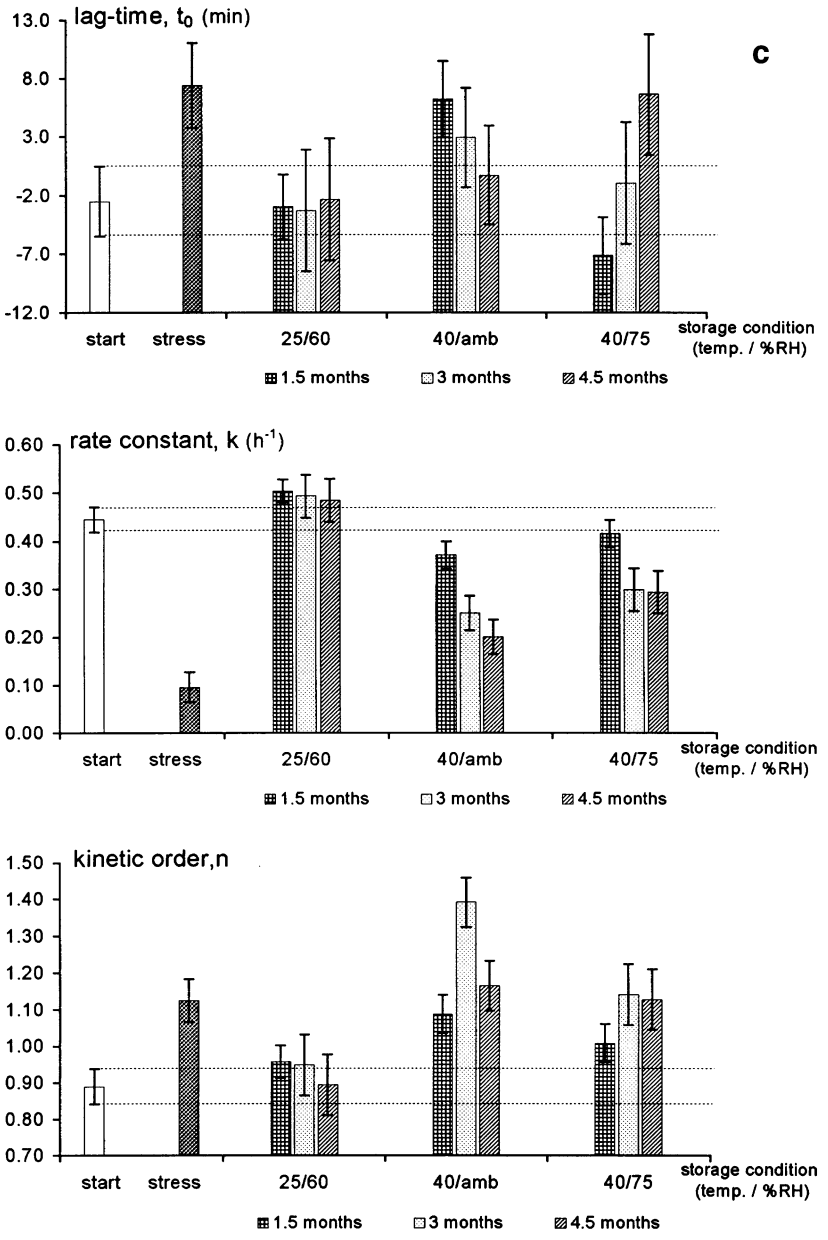

Fig. 3.

'stress' storage (Table 2). This behaviour indicates that in spite of some membrane damage the retarding effect of a dry hard tablet core of the non-disintegrated tablet dominates the last part of the profile. The release profiles in Fig. 2b verify that explanation and besides, it shows that the increased MDT for the 'stress' storage is caused by a very slow termination phase. As summarized in Table 2 there is consistency between the mechanism of 'stress' and of storage at 40/amb. However, the TCD and ΔMDT columns discover that quantitatively the 'stress'-effect is more significant.

Table 2
Survey of changes during stability test of IBU-PVP tablets, IBU-CMC tablets and ASA tablets

Tablet	Storage time	°C/% RH	t_0	k	n	TCD (%)	ΔMDT (%)
IBU-PVP	10 Days	50/amb	↑	↓	↑	—[a]	—[a]
	6 Months	25/60	—	—	—	2	1
		40/amb	↑	↓	↓	35*	19*
		40/75	↑	↓	—	21*	15*
IBU-CMC	10 Days	50/amb	↑	↑	↑	235*	100*
	6 Months	25/60	—	—	—	9	6
		40/amb	↑	↑	↑	50*	2
		40/75	↑	↑	—	33*	3
ASA	21 Days	50/amb	↑	↓	↑	485*	506*
	4 1/2 Months	25/60	—	—	—	9	−8
		40/amb	—	↓	↑	195*	201*
		40/75	↑	↓	↑	101*	102*

The parameter changes are from Fig. 3. The ΔMDT is calculated by Eq. (3) and TCD by Eq. (5).
For the ASA tablets the differences between TCD and ΔMDT (without sign) is due to random errors as all three contributions to ΔMDT (Eq. (4)) are positive numbers.
[a] As $n>2$ for the tablets after stress storage, no finite values of TCD and ΔMDT exist.
* Denotes statistical significant values.

The results for TCD and ΔMDT for tablets stored at 40/amb and 40/75 clearly illustrate the strength of using TCD to supplement ΔMDT for overall quantification of unstableness. The ΔMDT data show good stability, whereas the TCD shows significant instability. Thus, the TCD is more useful to summarize the effect of changes in t_0, k and n. The reason the MDT remains unaffected by the storage is that the increases of n and t_0—that make MDT grow—are counteracted by the increased k—that reduces MDT.

3.5. Multiparticulate ASA tablets.

The release profiles in Fig. 2c show significant instability for ASA tablets stored at 40/amb and 40/75 and a huge effect of 21 days of storage at 50/amb. Slow and incomplete disintegration was observed during dissolution tests and is most likely the cause of the increased t_0, decreased k and increased n. However, as appears from Table 2 and Fig. 3c, the aging mechanism of the 'stress'-condition (i.e. 21 days at 50/amb) differs from that seen after storage at 40/amb as this condition does not affect t_0. Tablets at 40/amb also did not disintegrate properly. An explanation for the unchanged t_0, in spite of slow disintegration, could be that the coated ASA crystals start releasing upon wetting when disintegration starts and the tablet loosens up. The difference between 40/amb and 50/amb is that at 50/amb a tablet core remains unwetted throughout the dissolution whereas at 40/amb a slow but complete disintegration is found.

4. Conclusions

4.1. Stability of the three tested products

Comparison of the three cases led to the following conclusions:

- For all three products disintegration troubles seem to be the predominant instability factor
- For all three products the high stress condition, 50/amb in 10 or 21 days led to slow and incomplete disintegration.
- The two ibuprofen formulations (IBU-PVP and IBU-CMC) showed instability at 40°C storage that involved interactions with the pellet cores.
- At 40/amb IBU-CMC was more stable than IBU-PVP which was more stable than ASA as indicated by ΔMDT. Using TCD the most

stable product was IBU-PVP and ASA the least stable.

- Effects due to changed membrane permeability were not identified. However, for IBU-PVP and ASA the reduced release rate may partly be caused by reduced permeability of the membrane.

4.2. Use of the order model for evaluation of dissolution stability

The Order Model was suitable for description of various storage induced changes. The model provided good fits of all curves evaluated, and the high precision of the parameter estimates enabled even small changes to be identified.

The statistical approach was very useful to the illustrated experiments as data interpretation was simple. However, the graphical part of the procedure limits the general applicability to relatively small experimental designs. For larger designs, the GLM approach suggested by Langenbucher (1991) should be considered.

Simple evaluation of the dissolution profiles supports Carstensen et al. (1992) and Dukes (1984) in the conclusions that dissolution stability is unpredictable. However, the demonstrated technique enables identification of the changes in each of the three parameters (t_0, k and n) as a function of the storage time. Continuous collection of storage data for different products evaluated by the Order Model will clarify the relation to storage time of the parameter values and their relation to different aging mechanisms and ideally in the long term allow prediction of the durability for a product with respect to dissolution stability.

The high stress condition, 50/amb in 10 or 21 days, was valuable as a reference for the stability evaluation as it demonstrated the effect on dissolution rate of slow and incomplete disintegration. However, this storage type did not predict all the observed effects of storage 4 1/2–6 months at 40/amb and 40/75.

The defined TCD-parameter was valuable to supplement the ΔMDT for quantification of dissolution changes—in particular if counteracting effects make the ΔMDT insignificant (cf. the IBU-CMC case).

Using ΔMDT and TCD relative to the start-MDT values enables comparison of unstableness across different stability trials and facilitate the accumulation of experience in this field.

Overall evaluation of the Order Model parameter changes is a sensitive analytical tool for characterization of dissolution stability. Contrary to evaluation of fixed time points dissolution data, it enables discovery of the mechanisms responsible for dissolution instability. Thus, the Order Model might turn out to be a valuable tool for the optimization of stability in product development in the future.

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