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AGING OF SUSTAINED-RELEASE FORMULATIONS OF AMOXYCILLIN AND GELUCIRE 64/02

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ABSTRACT

Sustained-release formulations prepared by fluid-bed coating with Gelucire 64/02 of direct acting granules were stored in two sets of conditions: controlled temperature and humidity and ambient temperature and humidity. The drug content and dissolution properties were determined after 2 and 4 months. Multifactorial ANOVA showed variations in the dissolution efficiency were influenced by the storage period and conditions and the percentage of excipient in the formulation. The dissolution media used gave marked modifications in the dissolution profiles. Modifications in the non-linear dissolution coefficients "k" and "n" are also analyzed.

INTRODUCTION

Gelucire excipient technology suffers from a lack of information on the excipient's behaviour during storage, which is particularly important since triglyceride excipients such as Gelucires can be prone to polymorphism and crystallization (1-7). The work described here studies modifications during the aging of sustained-release formulations of amoxycillin prepared by fluid-bed coating, with Gelucire 64/02 as a coating material.

MATERIALS AND METHODS

a) Preparation of the Formulations: Formulations containing 18%, 23% and 28% of Gelucire 64/02 were prepared as described in a previous work (8).

b) Storage Conditions: Formulations were stored under two sets of conditions: "controlled" or C.C (40ºC and 70% relative humidity), and "ambient" or C.A (the temperature and humidity in the laboratory about 20ºC). After two and four months, the drug content was determined (9) and dissolution tests were carried out in an Apparatus nº2 (USP XXII Ed.) at 37ºC and 200 r.p.m.. The dissolution media were artificial gastric and intestinal juices without enzymes (USP XXII Ed.). In gastric juice, to ensure reliable results the tests were carried out for a reduced length of time of three hours due to the degradation that amoxycillin undergoes in acid media (10).

c) Treatment of Results:

c.1) Dissolution efficiency was calculated according to Khan and Rhodes (11). The dissolution efficiencies for the tests in gastric juice and intestinal juice were termed D.E.(3h) and D.E.(8h), corresponding to the length of the test. An assessment was carried out for how each factor contributed to the alterations produced. The parameter chosen was "Var D.E." where:

Var D.E. = D.E. aged formulation - D.E. initial formulation.

Multifactorial ANOVA was used to test for the part played by percentage of excipient in the formulation, storage period and conditions and their interactions in the variations observed with respect to time zero. The test for the minimum significant difference was also applied.

c.2) Referring to other studies (12-15), we have calculated the non-linear dissolution parameters, "k" and "n", whose relevance can be gathered from the expression:

$$\% \text{ dissolved} = k\, t^n$$

The coefficient "n" is related to the release mechanism of the drug from the formulation and "k" to the rate at which this process takes place. For this study, they were estimated by linearisation for each test, and compared by a non-parametric test (16), the Friedman test.

RESULTS

Storage practically did not modify the drug content. In contrast, these conditions gave large alterations in the release of the drug (Figs. 1-4).

a) Formulation prepared with 18% Gelucire. In intestinal juice, storage in the ambient conditions gave a progressively slower release rate of the drug compared to a faster release rate in the controlled conditions (Fig.1). In gastric juice, however, release was delayed with respect to the initial formulations independent of the storage period and conditions (Fig.2).

b) Formulation prepared with 23% Gelucire. In the two dissolution media (Fig.3), drug release was faster than in the initial formulation, in the case of storage in the controlled conditions, and slower in the case of the formulations stored in ambient conditions.

c) Formulation prepared with 28% Gelucire. In this case the results, though not so clear, show a tendency for release to be slower at two months than at four months for either of the storage conditions (Fig.4).

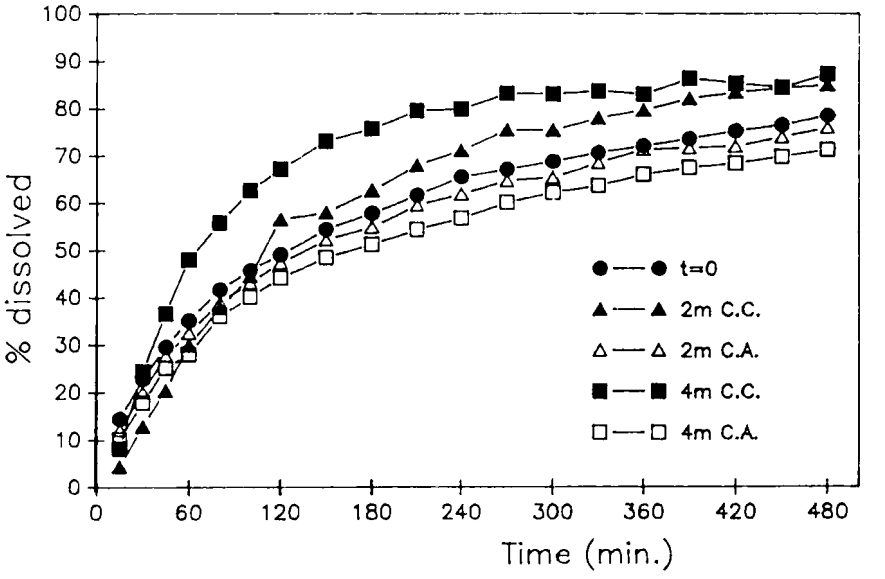

FIGURE 1
Amoxicillin Dissolution Profiles obtained in Intestinal Juice, with the formulation containing 18% (64/02).

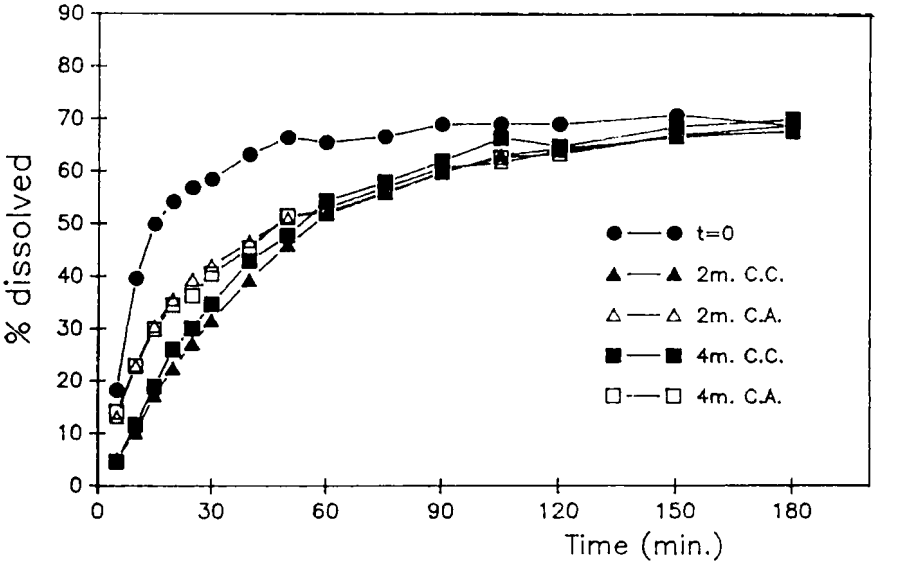

FIGURE 2
Amoxicillin Dissolution Profiles obtained in Gastric Juice, with the formulation containing 18% (64/02).

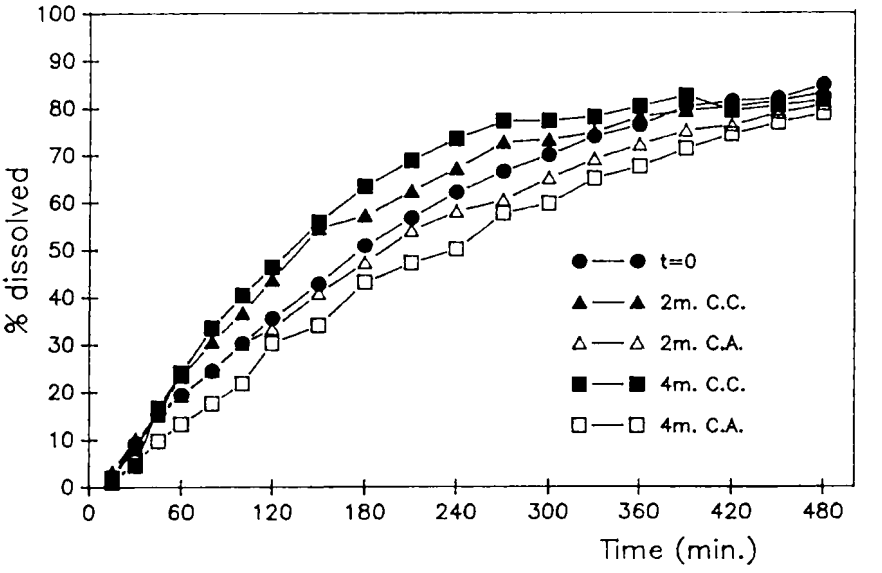

FIGURE 3
Amoxicillin Dissolution Profiles obtained in Intestinal Juice, with the formulation containing 23% (64/02).

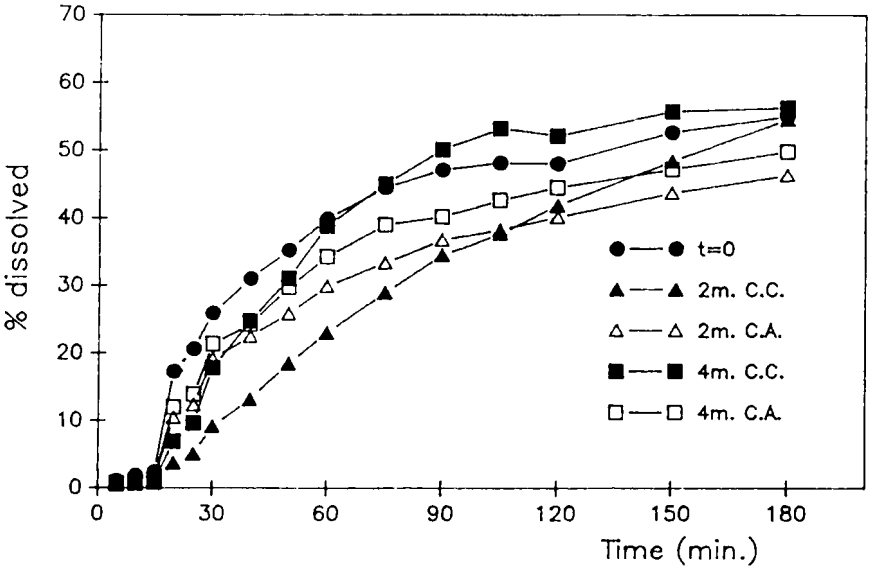

FIGURE 4
Amoxicillin Dissolution Profiles obtained in Gastric Juice, with the formulation containing 28% (64/02).

TABLE 1
Multifactorial ANOVA and Minimun Difference Test Results for D.E.(8h) and D.E.(3h).

Var.D.E.(8h)		
Mean effects		
Time	$F_{(1,36)} = 33.79$	< 0.01
Conditions	$F_{(1,36)} = 222.77$	< 0.01
64/02 Level	$F_{(2,36)} = 4.30$	< 0.05
Interactions		
TimexCond.	$F_{(1,36)} = 28.18$	< 0.01
TimexLevel.	$F_{(1,36)} = 24.01$	< 0.01
CondxLevel.	$F_{(2,36)} = 9.57$	< 0.01
CondxLevelxTime	$F_{(2,36)} = 8.48$	< 0.01
$\alpha = 0.01$ 2m. 4m.	18% 23% 28%	C.C. C.A.
Var.D.E.(3h)		
Mean Effects		
Time	$F_{(1,36)} = 32.62$	< 0.01
Conditions	$F_{(1,36)} = 32.65$	< 0.01
64/02 Level	$F_{(2,36)} = 52.06$	< 0.01
Interactions		
TimexCond.	$F_{(1,36)} = 0.80$	N.S.
TimexLevel.	$F_{(2,36)} = 8.82$	< 0.01
CondxLevel.	$F_{(1,36)} = 23.21$	< 0.01
CondxLevelxTime	$F_{(1,36)} = 0.25$	N.S.
$\alpha = 0.01$ 2m. 4m.	18% 23% 28%	C.C. C.A.

Multifactorial ANOVA and the test for the minimum significant difference (Table 1) showed percentage of Gelucire, storage period and conditions and the interactions among these factors explained the variations observed in Var D.E..

In gastric juice, "k" and "n" for formulations stored in controlled conditions were statistically different to those corresponding to storage in ambient conditions ($\alpha < 0.01$) (Table 2). In intestinal juice, the same result was obtained for "n" ($\alpha < 0.05$), but not for "k". No differences were found, nevertheless, between "k" and "n", in both dissolution media, at two months and at four months.

DISCUSSION

The absence of modifications in the drug content is in agreement with the characteristics of amoxycillin trihydrate in the solid state (17).

TABLE 2
Friedman Test Results

Coefficient	Medium	Treatment	Fr	α
k	Gastric	Conditions	24	0.01
k	Gastric	Time	1.5	N.S.
k	Intestinal	Conditions	2.6	N.S.
k	Intestinal	Time	1.5	N.S.
n	Gastric	Conditions	24	0.01
n	Gastric	Time	0	N.S.
n	Intestinal	Conditions	6	0.05-0.01
n	Intestinal	Time	0.6	N.S.

Since the non-linear dissolution coefficients were estimated by regression, analysis was limited to comparing whether their values at 2 and 4 months, in controlled and ambient conditions, were equal or not. It was found that only formulations stored in different conditions differed in the values of "n".

The implication is that different storage conditions give different release mechanisms in both gastric and intestinal juice. Nevertheless, "n" is the same for the formulations at four months and two months aging. The non-linear dissolution coefficient related with the rate of release, "k", is different for the formulations stored in different conditions when assayed in gastric juice, but not when assayed in intestinal juice. Values of "k" at 2 months and 4 months were not different in either of the dissolution media.

Possible causes of these variations may be modifications in either the amoxycillin or the excipient. In other studies, faster and slower drug release profiles have been observed (4, 5, 7, 18, 19) Different explanations have been offered: Progressive drug crystallization (20), drug transformation into a more stable allotropic form (21) and polymorphism and partial melting of the Gelucire during storage (7). Another cause of alterations in drugs

release from fatty matrices is progressive separation of the components of the matrix system (5). Gelucire excipients contain mixtures of palmitic and stearic esters (22). The triglycerides solidify in layers after melting and crystallize slowly (6). Temperatures around 60ºC are reached in the preparation of the formulations so that the Gelucire could melt during the process and, hence, suffer this slow crystallisation. Thus, as the fatty excipient crystallizes, it displaces the hydrophilic drug (2, 5).

Unfortunately, it was not possible to confirm any of these processes by techniques such as differential scanning calorimetry, since amoxycillin decomposes upon melting. Neither has X-ray diffraction been of help, and a similar failure of this technique to add information has been noted in other, similar studies with Gelucires (21, 23). Considering that nothing was added as to the causes of these alterations, the results obtained by the two techniques are not included.

Remaining as possible causes of the alterations observed are the slow crystallisation of the excipient and the drug, which will have opposing effects. The former process would preferably take place in the formulations stored at 40ºC and 70% humidity, since they would allow the Gelucire to partially melt; the latter process could account for the fall in release rate in the ambient conditions. Hence, there seems to be an explanation for the results obtained in intestinal juice with the formulation prepared with 18% Gelucire and in the two media with the formulation containing 23% Gelucire.

Nevertheless, with the formulation containing least Gelucire (18%) in gastric medium, which is a medium in which control of release is much lessened, different results are obtained. The solubility and release rate of amoxycillin are much greater in gastric juice than in intestinal (10, 24), so that it may be supposed that in this case, those factors reducing the solubility of the drug are more important. Apart from this, in this formulation more water may be retained because of the smaller percentage of fatty coating (25).

The further modification of values associated with increasing the percentage of Gelucire to 28% leads us to suspect, not unsurprisingly, that more variables are involved in

the processes, such as changes in porosity, coating, etc., that we have not been able to resolve.

Given that results differ by medium (different solubilities of drug) and percentage of Gelucire, we suppose that in the aging process, there are intervening factors affecting both the excipient and the drug, with one or the other being more strongly affected depending on the Gelucire level and modifications being more or less showed depending on the medium.

CONCLUSIONS

Storage in the two sets of conditions described leads to marked alterations in the release profiles of the drug that are illustrated by changes in the dissolution efficiency and the non-linear dissolution coefficient "n". These alterations are the result of a range of processes, showing the influence of time, conditions and percentage of Gelucire included in the formulation. To finish, it seems that the behaviour observed in the aging of the formulations lies in the way of these systems reaching some sort of clinical use.

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