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EFFECT OF FREEZER PROGRAMS ON REAL-TIME STORAGE RESULTS OF DISSOLUTION PROFILES

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ABSTRACT

Carstensen and Rhodes[1] have suggested that when, in stability programs, assays cannot be performed immediately after the protocol-designated storage time, then freezing them until such a time when assays can be performed would be a reasonable manner to retain the protocol schedule. They caution, however, that such a procedure may not be valid for dissolution data. The article to follow deals with real-time data showing that such a process is feasible for Nalidixic Acid tablets (and presumably for other tablets as well), and that, furthermore, the dissolution pattern would seem to be "frozen" as well.

INTRODUCTION

In the conducting of stability studies the problem always exists that when the time has come to remove a particular drug dosage unit from from storage (the pull-down date), the analytical component of the program may be overburdened, and that the assay, hence, cannot be carried out immediately. There would seem to be a

reasonable, acceptable interval between pull-time and assay-time of ±0.5 months, but this, frequently, is not sufficient to overcome scheduling problems. The argument is often forwarded that one may simply pull a sample (and this could, for instance, be a sample kept at Joel Davis[1] conditions[a]) at a date, equivalent to ß months, and if it is kept at controlled room temperature (e.g. in the analytical department) for another q months, then if it is assayed after ß+q months, then the sample could simply be treated as a ß month old sample. The argument is that when the regression lines are drawn for the stability data, treating a ß+q month data point as a ß-month data point will tilt the extrapolations unfavorably from the company's point of view.

This method, however, is at best questionable, because it confounds the statistical treatment with an uncontrollable bias, and it also may give rise to outliers, which, indeed may be treated as such, although, had they been assayed at the given time, would not have been outliers.

Rhodes and Carstensen[2] suggested that rather than letting samples await assay at laboratory temperature, they could be frozen till such a time when they were to be assayed. A separate study with real-time freezer points at e.g. one year at 5°F would then show that no degradation had occurred in that period of time, so that storing for ß months at room temperature (for instance) and q' months at 5°F, would, stability-wise, be equivalent to simple ß months storage at room temperature. They cautioned, however, that this procedure might not be valid for dissolution testing.

EXPERIMENTAL

Samples of batches of Nalidixic Acid tablets, 1 gram, made in production size scale, on production equipment and using production personnel was subjected to chemical and dissolution testing after the following schedule: One sample was stored at CRT conditions for a total of 5 months and 5 days and then assayed. A sample for

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[a] 40°C/75%RH

Table I. Dissolution Data for Several Production-Size Batches of Nalidixic Acid Tablets.

Batch #	Q_{30}-Values (Percent Dissolved)				
	Months at Controlled Room Temperature				
	Initial	3	9	12	18
A[a]	97.4	90.9	92.6	96.2	95.4
A	97.4	93.5	94.9	97.0	94.0
B[a]	97.0	97.1		102.6	93.8
B	97.0	95.3	100.5	104.0	93.9
C[a]	97.7	94.2	93.3	94.8	91.3
C	97.7	95.8	94.7	92.1	93.0

[a]The two batches denote different bottle sizes. Unsuperscripted letters denoted 750 mL for a count of 500, and superscripted letters denote 200 mL for a count of 100.

comparison was frozen for one month, then kept at room temperature for 2 months and 5 days, then frozen again for one month, and then stored for one month at CRT , and then tested for dissolution. The former sample will be denoted "CRT" in the following, and the latter will be denoted "Frozen".

The (USP) dissolution test consisted of determining the amount (percent) dissolved after 30 minutes (Q_{30}) in a medium consisting of USP phosphate buffer containing 20% of methanol. The dissolution volume was 900 mL at 60 RPM.

RESULTS AND DISCUSSION

Table I shows stability data of the general test for dissolution used in the routine stability program for Nalidixic Acid tablets.

Both paired t-tests and non-parametric tests fail to show a difference in the Q-values over the 18 months at the CRT conditions

shown, i.e. (a) the 18 month Q-value changes are sufficiently small to defy analytical detection. The only possible exception to this statement is that the Q-values at longest time point (18 months) does show a significant (albeit rather small) decrease when compared to the initial values.

In order to challenge the test as much as possible, a dissolution profile was obtained by submitting samples of batch A[a] to multi-point dissolution testing after 5 months at CRT and 5 months frozen. The results are shown in Table II below:

Table II. Results of CRT versus Frozen Cycling for Nalidixic Acid 1 gram Tablets. 12 Tablets from Batch A[a] Used for the Study.

Time (min)	Percent Dissolved (Avg of12 Tablets)		S.E.M.		95% Confidence Limits	
	Frozen	CRT	Frozen	CRT	Frozen	CRT
0	0	0				
10	86.9	83.5	0.9	1.1	2.0	2.4
20	101.0	93.0	0.66	0.66	1.4	1.4
30	104	94.6	0.52	0.67	1.1	1.4
45	104.3	95.9	0.46	0.66	1.0	1.4

These data are plotted in Fig. 1 below. It is seen that there is a slight slowing of the product stored at room temperature vis-a-vis the frozen cycle data.

It is noted that the dissolution data after 3 and 9 months storage at room tempearture in Table I do not differ significantly from initial data. However, comparison of room temperature data with the 5°F data in Fig. 1 shows that there is a slight degree of slowing down in the CRT samples.

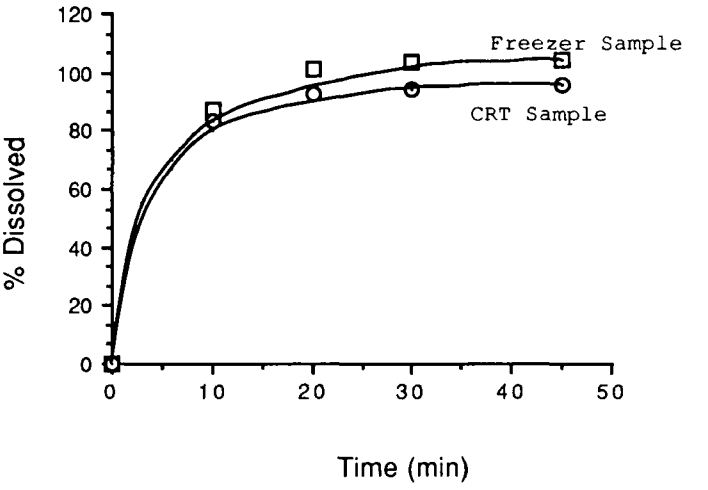

Fig. 1. Dissolution Data of Samples of Nalidixic Acid 1 gram tablets after 5 months at CRT and 5 months cycled at 5°F.

It is also noted that it is not possible from the data in Table I, to state that there is an ever so slight slowing down after five months, i.e. the use of the 5 Mo at 5°F reference is necessary to make such a conclusion. It has been pointed out in literature, that such changes in dissolution are prone to take place in the first months of storage only, i.e. level off rapidly upon storage [3] and are frequently referred to as a "leveling effect".

In any event, the product, although it appears to change ever so slightly in dissolution profile does so well within established limits. The data are presented simply to emphasize that the 5°F test, in this case, is useful, and probably is so in many cases, since it will allow monitoring of the magnitude of changes that are, otherwise, not possible to observe.

The reason that it is not possible to monitor the changes on storage without a freezer control (unless the changes are drastic) is the same as the reason for using an internal standard in chemical analysis. Most stability considerations consider the precision of assay and test methodology to be calender-time independent. There is abundant evidence[4] that this is not so, and the cited example is just such a case.

SUMMARY

1. Dissolution characteristics of Nalidixic acid show a very slight decrease in the Q_{30}-value after storage for 18 months at room temperature.

2. When 5 months old samples stored at controlled room temperature were compared with 5 months old samples stored at 5°F, this slight difference was evident.

3. A 5°F reference sample, in this case, is therefore quite useful, since it allows monitoring of very slight changes in dissolution profiles.

REFERENCES

1. Davis, Joel, Presentation at the 6th Annual Meeting of The Regulatory Affairs Professionals Society, Hyatt Regency, Washington, D.C., September 16, 1982.

2. J.T.Carstensen and C.T.Rhodes, (1986), Drug Dev. Ind.Pharm., 12:1219

3. J.T.Carstensen: Drug Stability, Principles and Practices", Marcel Dekker, N.Y., 1990, pg. 390

4. J.T.Carstensen: Drug Stability, Principles and Practices", Marcel Dekker, N.Y., 1990, pg. 491