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PELLICULE FORMATION IN GELATIN CAPSULES

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Hard and soft gelatin capsules are used extensively in the pharmaceutical industry. Hard shell capsules often provide a means of moderating anhydrous handling of a moisture or pressure-sensitive material, (only "moderately," because there is an equilibrium moisture content of the gelatin with which the powder blend must be compatible).

Soft gelatin capsules provide a method of orally administering, for instance, a water-insoluble drug substance in solution state. Although hypothetically, one might argue, in the later case, that the drug would precipitate out in the stomach, bioavailability studies in several cases have shown such systems to work. Dilution factors in the stomach fluids and slow nucleation of the drug substance are some of the reasons for this behavior.

It is the general concept that once the capsule enters the stomach, the gastric juice rather rapidly digests the gelatin, and presents the capsule contents to the gastric environment for the process of dissolution.

Gelatin is known to interact with aldehydes, forming cross-links presumably by way of a type of reaction, symbolized as:

$$RNH_2 + R'CHO \rightarrow RN{:}CR' + H_2O \quad (1)$$

Imines and ketones are capable of similar cross-linking. In the case of hard gelatin capsules, such an interaction at times gives rise to the formation of a very thin film

during a dissolution test in USP hydrochloric acid buffer. This film does not disrupt easily by gentle agitation and is usually referred to as a pellicule. It is mechanically weak and can easily be punctured.

In a dissolution test in hydrochloric acid buffer, as now prescribed by the USP, such films will not disrupt in the dissolution apparatus, and the Q-values will drop often to the point of rejection level.

The same holds true for soft shell capsules, even more so in such a case, because often the liquid containing the drug substance is polyoxyethylene glycol, which can form minute amounts of aldehydes which will then, via Eq. (1), promote the pellicule formation.

Elevated temperatures increase the rate with which the cross-linking occurs. It is, therefore, often the case that a capsule product will fail the Guidelines Accelerated test [c] (using hydrochloric acid buffer as a test medium), but be quite satisfactory at controlled room temperature storage. This may be of little practical consequence because a failure in the Joel Davis test should still (according to the 1987 Stability Guideline) allow regulatory blessing if the real time tests result in satisfactory Q-values.

Prior to the 1960s the pellicule formation presented no testing problem, because the dissolution medium contained pepsin and the pellicule never manifested itself. The film (unless of extensive dimensions) is rapidly digested by pepsin, and hence presents no testing problem in case of enzyme-containing test media.

The in-vitro/in-vivo relevance of using hydrochloric acid buffer must be questioned and the test is undoubtedly over discriminating in many cases of both hard and soft gelatin capsules. After all, the capsules in-vivo arrive at an environment where the gastric contents almost invariably contain enzymes. [d]

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[c] The test consists of 3 months storage at 40°C and 75% RH.

[d] It is, of course, not impossible (albeit unlikely) that there are cases where in-vivo failure also implies in-vitro failure.

Chafetz[1] attempted to disprove a general in-vitro/in-vivo correlation relevance [e] by monitoring the behavior of pelliculating hard shell capsules in the stomach. He found no visual difference between pelliculated and non-pelliculated capsules. Although it may be argued that there was no attempt in this study to establish the severity of the pelliculations (e.g., the dimensions of the film), it constitutes an argument in favor of the view voiced above. The two other shortcomings of the Chafetz study is that (a) it might be compared with the argument that just because a tablet disintegrates it does not necessarily allow the contents to dissolve. (b) it did not propose a test that had in-vitro/in-vivo correlation relevance.

Such a test would be inclusion of enzymes in the test medium, and the intent of this note is to call attention to the logic of such an approach. There are cases where FDA has approved ANDA's using enzyme dissolution technology, but presently the USP does not call for the use of enzymes.

From a scientific point of view, one might argue that the way of establishing a full rationale for the use of enzymes would be to, by way of a Joel Davis environment, create a batch of capsules that pelliculated in hydrochloric acid but not in medium with enzymes, and then establish bioequivalence with (non-pelliculated) controls (e.g., samples stored at CRT).

This, however, would be an expensive alternative to simply claiming that the capsules complied with specifications when stored at CRT and basing (as one would in any case) the room temperature expiration period on room temperature data. If the capsules also pelliculatd in hydrochloric acid at room temperature, but not in medium with enzymes, then only a bioavailability study would resolve the question.

Such a situation might well occur by itself sometime in the future, but to the authors' knowledge it has not yet happened.

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[e] The expression "correlation relevance" is used here to imply how well an in-vitro test mimics what actually happens in-vivo.

We are also concerned that in recent years some FDA investigators have been advocating that pharmaceutical companies retain stability samples designated for storage at controlled room temperature at 30± 2°C rather than 25°C. This view does not appear to be in line with present USP policy and is clearly in disharmony with EC requirement. Storage at 30°C rather than 25°C can greatly exacerbate the impairment of dissolution from hard gelatin capsules. Since 30°C is not the average temperature of CRT but the extreme such failures in dissolution may, in many instances, be an artifact of no real practical significance. We hope that this problem can be resolved in the very near future.

REFERENCES

1. Chafetz, L., Hong, W.H., Tslifonis, D.C., Taylor, A.K. and Philip, M. (1984), J. Pharm. Sci., 73:1186.