Digoxin Tablets Dissolution Test

The Communication to the Editor from Ylitalo *et al.*[1] in the July 1975 issue and, to a lesser degree, the earlier article by Klink *et al.*[2] appeared to embody a basic misunderstanding of compendial specifications.

Specifically, both of these articles report findings to the effect that certain batches of digoxin tablets failed to pass the dissolution specifications in the USP but yet were found on *in vivo* testing to give satisfactory serum concentrations of the drug.

Although the respective authors did not explicitly so state, the implications were that the USP specification was unsatisfactory or unsuitable and, specifically, that the dissolution requirement did not correlate with *in vivo* performance.

Dissolution specifications, as in the case of all other *in vitro* specifications in the official compendia, are intended to be established at a level, or to be designed in a manner, so that all clinically unsatisfactory products will be excluded. In doing so, it is recognized that, to provide such a level of assurance, at least some otherwise clinically acceptable lots will be excluded also.

For example, typical tablet monographs will specify that the assay show between 95 and 105% of the label amount of the active ingredient to be present. In establishing this tolerance level, it is recognized that a lot assaying 93 or 90%, or perhaps even 85%, may be clinically satisfactory but will nonetheless be rejected on the basis of this *in vitro* specification.

The point is that we do not generally have dose–response information that is so precise, or control over the biological system that is so complete, that a broader range can be safely established. As a consequence, a specification is adopted based upon the biological information that is known, and the tolerances are then drawn sufficiently tight so as to err on the safe side.

Consequently, the batches of digoxin tablets described by the above-mentioned authors were formulated in a manner that fell into a gray zone, where they were not good enough to pass the compendium *in vitro* specification but yet were not quite bad enough to exhibit *in vivo* unsuitability.

In conclusion, the two reports cited here should not be interpreted as reflecting adversely on the USP digoxin tablet specification. On the contrary, these reports demonstrate that the specification is sufficiently stringent that products passing the test can be regarded with confidence as being biologically and, therefore, clinically satisfactory.

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[1] P. Ylitalo, G. Wilén, and S. Lundell, *J. Pharm. Sci.*, **64**, 1264(1975).
[2] P. R. Klink, R. I. Poust, J. L. Colaizzi, and R. H. McDonald, Jr., *ibid.*, **63**, 1231(1974).