The Effect of Pancreatin on the Dissolution Performance of Gelatin-Coated Tablets Exposed to High-Humidity Conditions

Terrence C. Dahl,[1,2] I-Lan T. Sue,[1] and Alicia Yum[1]

Received January 19, 1990; accepted October 10, 1990
KEY WORDS: gelatin-coated tablets; acetaminophen dissolution; pancreatin; humidity; storage.

INTRODUCTION

Recent experiences in this laboratory indicate that high humidity can adversely affect the *in vitro* disintegration and resultant drug release from hard gelatin capsules. *In vitro* dissolution changes as a result of high humidity have also been observed elsewhere for capsules containing chloramphenicol (1,2), tetracycline (2), nitrofurantoin (3), and either water-insoluble or relatively water-soluble agents (4). During distribution, commercial products may be exposed to high humidity. This may lead to changes in bioavailability and/or efficacy. Martin (5) reported how humid storage conditions destroyed the clinical efficacy of phenytoin capsules. Chavetz *et al.* (6), however, found that poor-dissolving gemfibrozil capsules exposed to high humidity were bioequivalent to those showing no film formation (i.e., good dissolvers).

A recent publication by Murthy *et al.* (7) demonstrated that hard gelatin capsule products tested in a dissolution medium containing enzymes would negate the deleterious effects of adverse storage conditions on the *in vitro* dissolution performance. Enzymes are present in the gastrointestinal fluids, therefore, the inclusion of enzymes may simulate the physiological conditions that an ingested dosage form would encounter during transit through the gastrointestinal tract (8).

In recent years, a gelatin-coated acetaminophen tablet was introduced to the marketplace. This dosage form also contains sodium starch glycolate (9), a disintegrant which should aid in the dissolution process. To determine how high-humidity exposure would affect the *in vitro* dissolution performance of this product, gelatin-coated acetaminophen tablets were exposed for several months to both room-temperature and high-humidity storage conditions. The product's dissolution performance in media with or without pancreatin was determined to assess whether the presence of the enzyme in the dissolution medium could override the storage effect of high humidity on this unique dosage form.

EXPERIMENTAL

Chemicals

Acetaminophen tablets (Tylenol Gelcaps, Lot DLR122, McNeil, Fort Washington, PA), acetaminophen, USP (Lot 0048985E984, Mallinckrodt, St. Louis, MO), sodium hydroxide, NF (Lot 5367KBAH, Mallinckrodt, St. Louis, MO), acetonitrile (Lot AV677, Baxter Health Care Corp., Burdick & Jackson, Division, Muskegon, MI), trifluoroacetic acid (Lot 49F-3519, Sigma, St. Louis, MO), hydrochloric acid solution 12M (Lot 3560KVTM-A, Mallinckrodt, St. Louis, MO, or Lot A48042, Baker, Phillipsburg, NJ), and pancreatin (Lot 36F-0632, Sigma, St. Louis, MO) were used as received. The pancreatin had activity at least equivalent to the USP specification.

Dissolution Testing

All dissolution tests were conducted according to the USP XXII Apparatus II (10). A dissolution apparatus (Hanson Research, Northridge, CA) equipped with USP paddles rotating at a speed of 50 rpm was used. The dissolution medium was 900 ml of either deionized water or a 1% (w/v) aqueous pancreatin solution maintained at 37°C. Sampling was performed at 11.3, 24.4, 37.5, and 60.0 min by an automated system. Samples were analyzed at a wavelength of 244 nm using a Model HP-8451A diode array spectrophotometer (Hewlett-Packard, Palo Alto, CA) if the dissolution medium was deionized water. The absorbance values were then compared to a standard calibration curve.

Pancreatin enzyme interferes with accurate UV analysis of the filtered samples so the concentration of drug in the dissolution medium was monitored by reverse-phase HPLC. The HPLC system was comprised of a Model D2000 integrator and Model 655A-40 autosampler (Hitachi, Tokyo), Spectroflow Model 400 pump and Model 757 detector (Kratos, Ramsay, NJ), and a 10-μm, 3.9 mm × 150-mm CN μ-Bondapak column (Millipore, Bedford, MA). The mobile phase (10% acetonitrile, 89.9% water, and 0.1% trifluoroacetic acid) was filtered through a 0.45-μm solvent-resistant filter (Millipore, Bedford, MA) prior to use. The mobile phase was pumped through the apparatus at a rate of 0.5 ml/min, and the UV detector set at 242 nm.

Samples were manually taken, filtered through a 0.45-μm solvent resistant filter, and then diluted 10-fold. The injection volume was 25 μl. The amount of acetaminophen dissolved was calculated by comparing the integrated peak area against known standards. The coefficient of variation for the method was less than 1% for the concentration range studied.

Stability Studies

Gelatin-coated tablets were either stored in the original commercial container at room temperature or placed in open petri dishes where they were exposed to a constant condition of 37°C/80% RH in a humidity chamber (Forma Scientific, Inc., Marietta, OH). The latter condition was chosen to accelerate physical changes. Samples were tested for their *in vitro* dissolution performance at 0, 1.5, 3.5, and 7.0 months.

[1] Syntex Research (R1-166), 3401 Hillview Avenue, Palo Alto, California 94304.
[2] To whom correspondence should be addressed.

0724-8741/91/0300-0412$06.50/0

RESULTS AND DISCUSSION

Effect of High-Humidity Storage Conditions on Dissolution of Gelatin-Coated Acetaminophen Tablets

Figure 1 illustrates the *in vitro* dissolution performance of gelatin-coated acetaminophen tablets tested in deionized water. The gelatin-coated tablets were stored up to 7 months at room temperature, however, there was no change in the *in vitro* dissolution performance.

Figure 2 shows how 1.5 months of high-humidity exposure begins to affect adversely the 11-min dissolution time point for a gelatin-coated acetaminophen tablet dosage form in water. Exposure to high humidity continues to cause slowing of acetaminophen release at 3.5 months of storage. During *in vitro* testing sheaths of gelatin could be seen peeling off the stressed tablets. The appearance of these sheaths is not surprising considering the acetaminophen tablet coating (dipping) process. It should also be noted that the standard deviation of the dissolution profile for the 3.5-month high-humidity sample was very large, especially at the 60-min time point. Four tablets did not dissolve and two tablets released a substantial amount of acetaminophen. Presumably, the latter was due to rupture of the sheaths. The 7-month high-humidity samples show significant reductions in both the amount released and the standard deviation at each time point, because the sheaths were well formed and no rupture of the sheaths was observed among the six tablets tested.

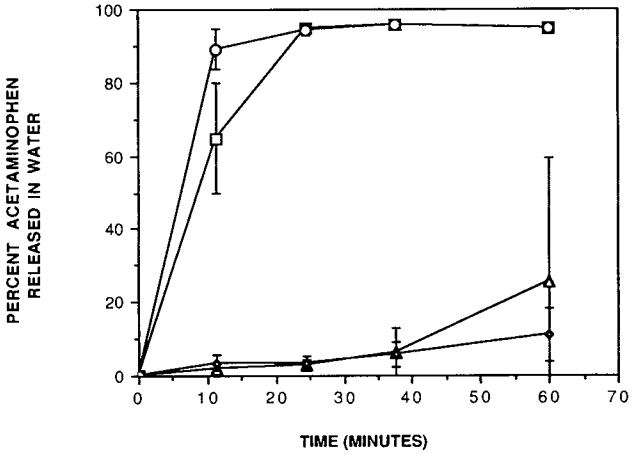

Fig. 2. Effect of high-humidity exposure (○, initial; □, 1.5 months; △, 3.5 months; ◇, 7 months) on the *in vitro* release of acetaminophen from gelatin-coated tablets stored in open petri dishes.

Effect of Pancreatin on Dissolution of Gelatin-Coated Acetaminophen Tablets

Recently Murthy *et al.* (7) demonstrated that dissolution media containing the enzyme, pepsin or pancreatin, would totally dissolve hard gelatin capsules exposed to either severe light or high-humidity storage conditions. The same phenomenon was observed when gelatin-coated acetaminophen tablets, stored in the humidity chamber for 7 months, were tested in a 1% aqueous pancreatin solution. Figure 3 shows that it took only 11 minutes to release 90% of the acetaminophen dose from the 7-month-old room temperature samples when either deionized water or a 1% (w/v) aqueous pancreatin solution was the dissolution medium. Figure 3 also clearly demonstrates the enhancement of acetaminophen release by using pancreatin in the dissolution medium versus plain water to test the 7-month high-humidity samples. At 11 min there was a notable difference between samples stored at room temperature versus high humidity. However, by 25 min those differences were nonexistent in dissolution medium containing pancreatin. It appears that the dissolution test is still relatively discriminatory, because the room-temperature samples and high-humidity samples behaved quite differently at early time points, even in dissolution medium containing pancreatin. Therefore, it is possible that *in vitro* drug release in the medium containing enzyme is still correlated with *in vivo* performance. If so, using a dissolution medium containing pancreatin or another enzyme could serve as a method to screen out poor-performing *in vivo* batches.

In vitro–in vivo correlations have been established with several therapeutic agents (11–17). Those correlations, which were retrospective in nature, involved correlating pa-

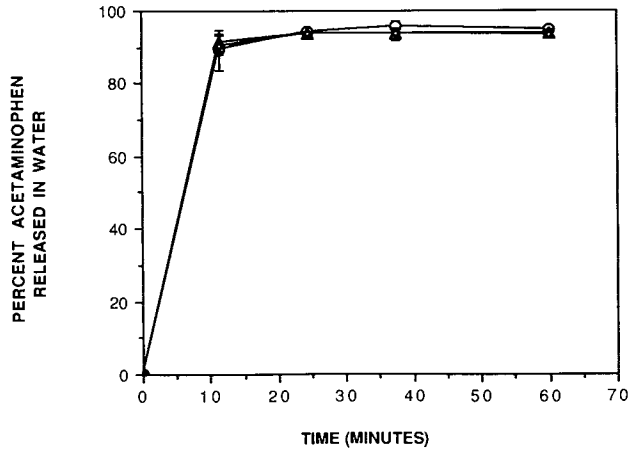

Fig. 1. Effect of room temperature storage (○, initial; △, 3.5 months; ◇, 7 months) on the *in vitro* release of acetaminophen from gelatin-coated tablets stored in HDPE bottles.

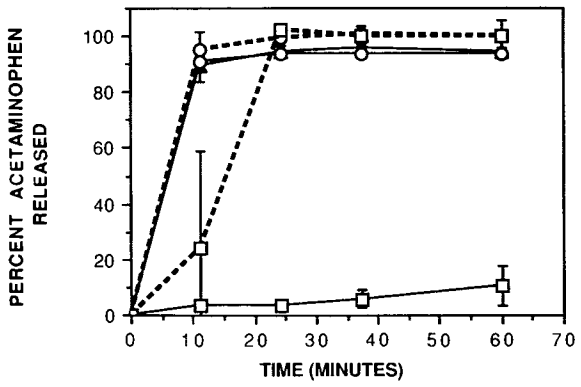

Fig. 3. Effect of dissolution media with pancreatin (dashed line) and without pancreatin (solid line) on the *in vitro* release of acetaminophen from gelatin-coated tablets stored for 0 months (△), for 7 months at room temperature (○), and for 7 months exposed to high humidity (□).

rameters such as urinary excretion and percentage dissolved (11,12), C_{max}/t_{max} and percentage dissolved (13–16), and AUC and percentage dissolved (17). Hence, it is critical to have a validated *in vitro* dissolution method, which can distinguish the batches performing differently *in vivo*. It would also be ideal to formulate a capsule or tablet dosage form, which will satisfactorily perform both *in vivo* and *in vitro*, regardless of storage conditions (light, high humidity, etc.).

CONCLUSION

This work demonstrates the effect of incorporating pancreatin into the dissolution medium to evaluate *in vitro* drug release from gelatin-coated tablets exposed to high-humidity conditions. The samples stored at room temperature showed no change in *in vitro* dissolution performance whether tested in water with or without pancreatin. Medium containing pancreatin improved the dissolution performance of the stressed gelatin-coated tablets, compared to dosage forms tested in deionized water. These results for gelatin-coated tablets are similar to those from previous work performed using hard gelatin capsules exposed to high humidity (7).

The technique of enzyme addition to the dissolution medium is controversial for a number of reasons. First, the incorporation of enzymes renders the analytical work more cumbersome. Second, the presence of the enzymes could bias the *in vitro* dissolution results so that no batches will fail. Although this work showed that the batch of gelatin-coated tablets would release all the acetaminophen within an hour, the method was still discriminatory enough to show the performance of the dosage form stored in high humidity was compromised. In any case, each product would have to be screened *in vivo* to determine the reliability of *in vitro* dissolution testing with and without the use of enzymes. It is conceivable that under certain conditions a capsule or gelatin-coated dosage form may not dissolve satisfactorily even in the presence of enzymes.

Previous work (7) and this work raise the question of the pertinence of *in vitro* dissolution testing in media without enzymes of hard gelatin capsule dosage forms or gelatin-coated dosage forms. This is especially true when dissolution is used as a physical stability tool. Since physiologic conditions include an attrition mechanism in the stomach to reduce the size of the gastric contents and the gastrointestinal mileu contains enzymes (8), *in vitro* dissolution test results in water or other buffer systems may not necessarily be relevant to *in vivo* performance for all gelatin capsule and/or gelatin-coated tablet products following storage at high humidity. Additional *in vivo* studies are needed to confirm this hypothesis.

REFERENCES

1. S. A. H. Khalil, L. M. M. Ali, and M. M. Abdel Khalek. Effects of ageing and relative humidity on drug release. *Pharmazie* 29(1):36–37 (1974).
2. P. York. The shelf-life of some antibiotic preparations stored under tropical conditions. *Pharmazie* 32(2):101–104 (1977).
3. H. W. Gouda, M. A. Moustafa, and H. I. Al-Shora. Effect of storage on nitrofurantoin solid dosage forms. *Int. J. Pharm.* 18:213–215 (1984).
4. K. S. Murthy, N. A. Enders, and M. B. Fawzi. Dissolution stability of hard-shell capsule products. The effect of exaggerated storage conditions. *Pharm. Technol.* 13(3):72–86 (1989).
5. E. D. Martin, R. J. L. Fraser, and I. Camens. Storage of phenytoin capsules. *Med. J. Aust.* 143:634–635 (1985).
6. L. Chavetz, W. Hong, D. C. Tsilifonis, A. K. Taylor, and J. Philip. Decrease in the rate of capsule dissolution due to formaldehyde from polysorbate 80 autoxidation. *J. Pharm. Sci.* 73(8):1186–1187 (1984).
7. K. S. Murthy, R. G. Reisch, Jr., and M. B. Fawzi. Dissolution stability of hard-shell capsule products. The effect of dissolution test conditions on in vitro drug release. *Pharm. Technol.* 13(6):53–58 (1989).
8. H. Minami and R. W. McCallum. The physiology and pathophysiology of gastric emptying in humans. *Gastroenterology* 84:1592–1610 (1984).
9. M. M. Schumacher and A. L. Dowd (eds.). *Physician's Desk Reference for Nonprescription Drugs*, 10th ed., Medical Economics Co., Oradell, NJ, 1990, pp. 598–599.
10. *United States Pharmacopeia XXII/National Formulary XVII*, United States Pharmacopeial Convention, Inc., Mack, Easton, PA, 1989, pp. 1578–1579.
11. T. R. Bates, D. A. Lamber, and W. H. Johns. Correlation between the rate of dissolution and absorption of salicylamide from tablet and suspension dosage forms. *J. Pharm. Sci.* 58(12): 1468–1470 (1969).
12. M. K. T. Yau and M. C. Meyer. *In vivo-in vitro* correlations with a commercial dissolution simulator. I. Methenamine, nitrofurantoin, and chlorothiazide. *J. Pharm. Sci.* 70(9):1017–1024 (1981).
13. J. G. Wagner, P. G. Welling, K. P. Lee, and J. E. Walker. *In vivo* and *in vitro* availability of commercial warfarin tablets. *J. Pharm. Sci.* 60(5):666–677 (1971).
14. V. P. Shah, V. K. Prasad, T. Alston, B. E. Cabana, R. P. Gural, and M. C. Meyer. Phenytoin. I. *In vitro-in vivo* correlation for 100-mg phenytoin sodium capsules. *J. Pharm. Sci.* 72(3):306–310 (1983).
15. M. C. Meyer, A. B. Straughn, G. Raghow, W. L. Schary, and K. S. Rotenberg. Absorption of phenobarbital from tablets and elixir. *J. Pharm. Sci.* 73(4):485–488 (1984).
16. A. B. Straughn, G. C. Wood, G. Raghow, and M. C. Meyer. Bioavailability of dyphylline and dyphylline-guaifenesin tablets in humans. *J. Pharm. Sci.* 74(3):335–337 (1984).
17. M. K. T. Yau and M. C. Meyer. *In vivo-in vitro* correlations with a commercial dissolution simulator. II. Papaverine, phenytoin, and sulfisoxazole. *J. Pharm. Sci.* 72(6):681–686 (1983).