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Comparison of the Dissolution of Metaxalone Tablets (Skelaxin) using *USP* Apparatus 2 and 3

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ABSTRACT

The purpose of this study was to evaluate the effect of pH on the dissolution behavior of metaxalone in the marketed product Skelaxin tablets. The dissolution was evaluated using United States Pharmacopeia (USP) dissolution Apparatus 2 and 3 at pHs ranging from 1.5 to 7.4. Results from these studies show that the dissolution of this product is pH dependent. At low pH (simulated gastric fluid, pH 1.5), the dissolution of metaxalone from Skelaxin tablets was less than 10% over 75 minutes; whereas, dissolution at pH 4.5 showed greater than 90% release in the same time period. These results were consistent for both Apparatus 2 and 3. This suggests that Skelaxin Tablets should be considered a delayed release dosage form.

KEYWORDS: Metaxalone, dissolution, pH dependence, apparatus 3

INTRODUCTION

The first published reports about the use of metaxalone as a skeletal muscle relaxant appeared in the 1960s.[1] Since then it has appeared in several reviews for this purpose, the most recent of which[2] asserts that "metaxalone has the fewest reports of side effects and no reports of major safety issues" (p. 63) as compared with other skeletal muscle relaxants. In addition, there seems to be continued interest in this product, possibly because of new indications.[3-5]

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Metaxalone is commercially available as a 400-mg tablet, brand name Skelaxin. This product was approved by the FDA in 1962.[6] It is interesting to note that the package insert for Skelaxin does not contain any patient dosing, pharmacokinetic, or formulation information. Nor is there an indication of whether the product should be taken with or without food. However, according to patent US 6 407 128 B1,[7] the bioavailability of Skelaxin increases if dosed with food.

According to AHFS Drug Information 2001,[8] "following oral administration of a single 800 mg dose of metaxalone, mean peak plasma concentrations are attained in 2 hours. The onset of action is usually within 1 hour and the duration of action is about 4 to 6 hours. The drug has a plasma half-life of 2-3 hours. Metaxalone is metabolized in the liver and excreted in urine as unidentified metabolites." (p. 1331) Although, there is not much information on the metabolism of metaxalone in the literature, the chemistry of the metabolic products was proposed by Bruce et al.[1] Several metabolites were identified, but no further information was found in the literature about the activity of these metabolites.

Chemically, metaxalone occurs as a white crystalline powder with a bitter taste that is insoluble in water and soluble in alcohol. There are no data published about the dissolution of the commercially available formulation (Skelaxin), nor is there a compendial method available.

Although metaxalone has been on the market for 40 years, there is relatively little known about the dissolution behavior of the marketed product, Skelaxin. These studies looked at the dissolution of metaxalone tablets with United States Pharmacopeia (USP) Apparatus 2 using water (pH undetermined), and 3 pH-controlled media: pH 1.5 simulated gastric fluid (SGF), pH 4.5, and pH 7.4 simulated intestinal fluid (SIF), with and without the addition of surfactant. The SGF and SIF were based on the standard USP solutions for simulated gastric and simulated intestinal fluids. In addition, several studies were done using USP Apparatus 3 (BioDis) with various pH gradients from pH 1.5 to pH 6.8. Apparatus 3 has the advantage of more easily assessing a pH effect as the tablets can be moved from one pH in one vessel to another pH in another vessel.

MATERIALS AND METHODS

Materials

Metaxalone tablets (400 mg Skelaxin, lot no. GS910FH, Mallinckrodt Inc, Hobart, NY for Elan Pharmaceuticals, Cedar Knolls, NJ) and metaxalone micronized (Aziende Chimiche Riunite Angelini Francesco, Aprilia [LT], Italy) were used as purchased. All water used was Poland Springs distilled water, which was evaluated for conformance to purified water USP. Sodium lauryl sulfate (SLS) (Sigma, St Louis, MO), sodium dihydrogen phosphate (Alfa Aesar, Ward Hill, MA), and all other chemicals were of analytical grade and were used as received.

Analytical Methods

Metaxalone was quantified by high-performance liquid chromatography (HPLC). The analytical column used was either a Waters NovaPak, C_{18}, 4 µm, 150 mm × 3.9 mm (Waters Corp, Milford, MA) or an Alltech Econosphere C_{18}, 5 µm, 4.6 mm × 150 mm (Alltech Associates Inc, Deerfield, IL). The mobile phase consisted of 0.005M sodium dihydrogen phosphate buffer:methanol (420:580). A flow rate of 1 mL/minute resulted in a retention time of 3.5 minutes. The peak area was recorded at 273 nm using either a UV 1000 or UV 6000LP detector (Thermo Separation Products, San Jose, CA) and converted to concentrations by comparison with external standards. Samples of 5 mL were removed from the dissolution vessel (either Apparatus 2 or 3), filtered through a Titan nylon 0.45-µm filter (Sun Sri, Wilmington, DE), and tested without further dilution.

Dissolution Studies

Dissolution studies were performed using either USP Apparatus 2 or Apparatus 3.

USP Apparatus 2 consisted of a Vanderkamp 600, 6-spindle dissolution tester (Van Kel Technology Group (Edison, NJ). All studies were run at 75 rpm, using 900 mL of media at 37°C. During assay development, it was seen that both water and pH 4.5 buffer produced incomplete dissolution results, only reaching about 50% in 75 minutes. Dissolution was shown to be more complete, reaching >90% in 75 minutes with the addition of up to 2% SLS to the dissolution media. Therefore, all dissolution studies using Apparatus 2 were carried out with dissolution media that contained 2% SLS.

USP Apparatus 3 consisted of a Bio-Dis III extended-release tester (model 25-1000, Van Kel Technology Group). All studies in USP Apparatus 3 were run using a 40-mesh, 0.405-mm polypropylene screen at 30 dips per minute, using 250 mL of buffer at 37°C. For these studies, the dosage form was removed from the vessel, SLS equivalent to 2% wt/vol was added to the vessel, and the contents were stirred with a magnetic stirring bar.

Dissolution was performed using the following media:

- water (undetermined pH)
- pH 1.5 (USP SGF without pepsin [0.05M sodium chloride adjusted to pH 1.5 with HCl])
- pH 3.0 (0.05M sodium chloride adjusted to pH 3.0 with HCl)
- pH 4.5 (0.05M sodium dihydrogen phosphate buffer adjusted to pH 4.5 with NaOH)
- pH 6.8 (USP SIF without pancreatin [0.05M sodium dihydrogen phosphate buffer adjusted to pH 6.8 with NaOH])
- pH 7.4 (0.05M sodium dihydrogen phosphate buffer adjusted to pH 7.4 with NaOH)

RESULTS

A comparison of Apparatus 2 dissolution results using 2% SLS in various media can be seen in Figure 1. After 75 minutes, at low pH (pH 1.5) the dissolution was minimal, with 7.2% ± 0.7% released. It was also incomplete at pH 7.4 with 55.7% ± 15.0% released. In contrast, the 75-minute dissolution in pH 4.5 was 96.3% ± 3.0%, and in water (unspecified pH) 91.9% ± 7.0%. These results clearly indicate that the dissolution of metaxalone from Skelaxin tablets is pH dependent.

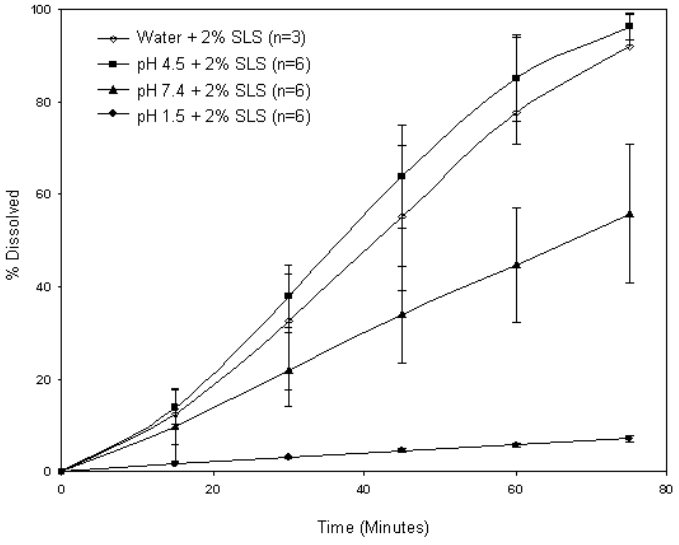

Figure 1. Dissolution of metaxalone tablets: *USP* Apparatus 2; paddles, 75 rpm.

Table 1. Dissolution of Metaxalone Tablets: *USP* Apparatus 3, Biodis*

Time (Hours)	pH	% Dissolved ± SD	pH	% Dissolved ± SD	pH	% Dissolved ± SD
1	1.5	1.8 ± 0.1	1.5	1.8 ± 0.2	1.5	2.7 ± 2.3
2	1.5	3.3 ± 0.1	1.5	3.5 ± 0.4	3.0	74.6 ± 8.7
3	4.5	78.8 ± 6.3	6.8	90.2 ± 4.5	4.5	87.4 ± 4.4
4	4.5	85.8 ± 2.2	6.8	96.4 ± 1.4	6.8	89.6 ± 1.8

*% Dissolved indicates the percentage dissolved after solubilization of vessel contents with 2% SLS. All values are mean ± SD (n = 7).

Since there was a clear indication of the pH dependence on the dissolution, experiments were conducted using USP Apparatus 3. Apparatus 3 has the advantage of more easily assessing a pH effect as the tablets can be moved from one vessel to another of a different pH. However, it is generally not practical to use surfactants in Apparatus 3 because of foaming. Therefore, these studies were carried out in the designated pH buffer, followed by solubilization of the vessel contents by the addition of 2% wt/vol SLS. Dissolution results using Apparatus 3 can be seen in Table 1. If the tablets are left at pH 1.5 in Apparatus 3 for up to 2 hours, there is no discernible dissolution (3.3% ± 0.3%). Not only is metaxalone not going into solution, but at low pH the tablet disintegration is insufficient to enable metaxalone solubilization after the addition of SLS. The results for pH profiles 1 and 2 indicate that after 2 hours at pH 1.5, if the pH is raised to 4.5, or to 6.8, appreciable dissolution is achieved (78.8% ± 6.3% and 90.2% ± 4.5%, respectively). In comparison to pH profile 3, if the pH is raised to 3.0 after 1 hour, there is appreciable dissolution at 2 hours (74.6% ± 8.7%). Thus, the release profile is highly pH dependent.

In comparison, the pH dissolution results were consistent between the 2 methods (Apparatus 2 vs Apparatus 3). Dissolution at pH 1.5 was consistently low with <10% release for up to 75 minutes with Apparatus 2 and for up to 2 hours with Apparatus 3. However, the dissolution was drastically improved at pH 4.5 with Apparatus 2, or within 1 hour of the pH change to pH 4.5 or 6.8 with Apparatus 3, with approximately 80% release in both cases.

Other studies performed in these labs indicate that the pH effect is formulation related rather than solubility related (G. Reilly, unpublished data, 2001).

CONCLUSION

Based on dissolution results in SGF using both Apparatus 2 and 3, metaxalone in the form of Skelaxin tablets does not dissolve at a low pH. This finding implies that in this formulation metaxalone presents itself as a delayed-release dosage form. If a patient takes the tablets on an empty stomach, it could be several hours before the product is exposed to a pH >3 that would effect its release. In addition, this might be responsible for the food effect seen in patent US 6 407 128 B1.[7]

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