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METHODS TO COMPARE DISSOLUTION PROFILES*

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The objective of this work was to apply several profile comparison approaches to dissolution data of four different metoprolol tartrate tablet formulations in order to quantify each method's metric for comparing dissolution profiles. Dissolution was performed using the United States Pharmacopeia (USP) monograph method on four formulations of metoprolol tartrate tablets. Two general approaches to compare dissolution profiles were examined: model-independent approaches and model-dependent approaches. The model-independent methods included ANOVA-based procedures, ratio test procedures, and pair-wise procedures. The model-dependent approaches included zero-order, first-order, Hixson-Crowell, Higuchi, quadratic, Weibull, Gompertz, and logistic models. It is concluded that the ratio test procedures, the pair-wise procedures, and several model-dependent approaches yielded numerical results which can possibly serve as objective and quantitative metrics for comparing entire dissolution profiles of the four metoprolol tartrate formulations.

Key Words: Dissolution; Metoprolol tartrate; Comparison; Dissolution profile comparison

THE CENTER FOR DRUG Evaluation and Research (CDER) at the Food and Drug Administration (FDA) recently released a guidance which set forth application information that should be provided to CDER to assure continuing product quality and performance characteristics of immediate release oral solid dosage formulations for specific post-approval changes (1). Commonly called SUPAC IR, this guidance has the major intent to reduce the number of manufacturing changes that require preapproval by FDA. Consequently, dissolution testing is a prominent feature of SUPAC IR requirements. In order for a pharmaceutical sponsor to take advantage of the benefits offered in the SUPAC IR guidance where Case B or Case C dissolution testing is required, a sponsor will need to demonstrate that the dissolution profiles of the product prechange and postchange are "similar." The objective of this work was to apply several profile comparison approaches to dissolution data of four different metoprolol tartrate tablet formulations in order to quantify each method's metric for comparing dissolution profiles.

*This manuscript represents the personal opinion of the authors and does not necessarily represent the views or policy of the agency.

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EXPERIMENTAL SECTION

Metoprolol Dissolution

Dissolution was performed on four formulations of 100 mg metoprolol tartrate tablets, Lopressor® (lot #JT4781, Geigy), and three formulations developed and manufactured at the University of Marlyand at Baltimore (UMAB) School of Pharmacy. Figure 1 shows the dissolution profiles of the metoprolol tartrate formulations. Dissolution was performed on six tablets of each formulation using the USP monograph method. Dissolution employed the basket method at 100 rpm. The medium was 900 ml of simulated gastric fluid without enzyme. Lopressor® was the most rapidly dissolving formulation. Dissolution samples were collected at 5, 10, 15, 20, 25, 30, and 45 minutes for Lopressor® and the two most rapidly dissolving test formulations, formula, #DF931007 and formula #DF931004. The slowly dissolving formula, #DF931011, was sampled at identical times plus at 60, 90, and 120 minutes. Formulas #DF931007, #DF931004, and DF931011 will be referred to as the fast, medium, and slow test formulations, respectively.

Model-independent Methods

The methods investigated to compare profiles can be classified into two categories: model-independent approaches and model-dependent approaches. For the model-independent methods, metoprolol dissolution data were used with modification. The per-

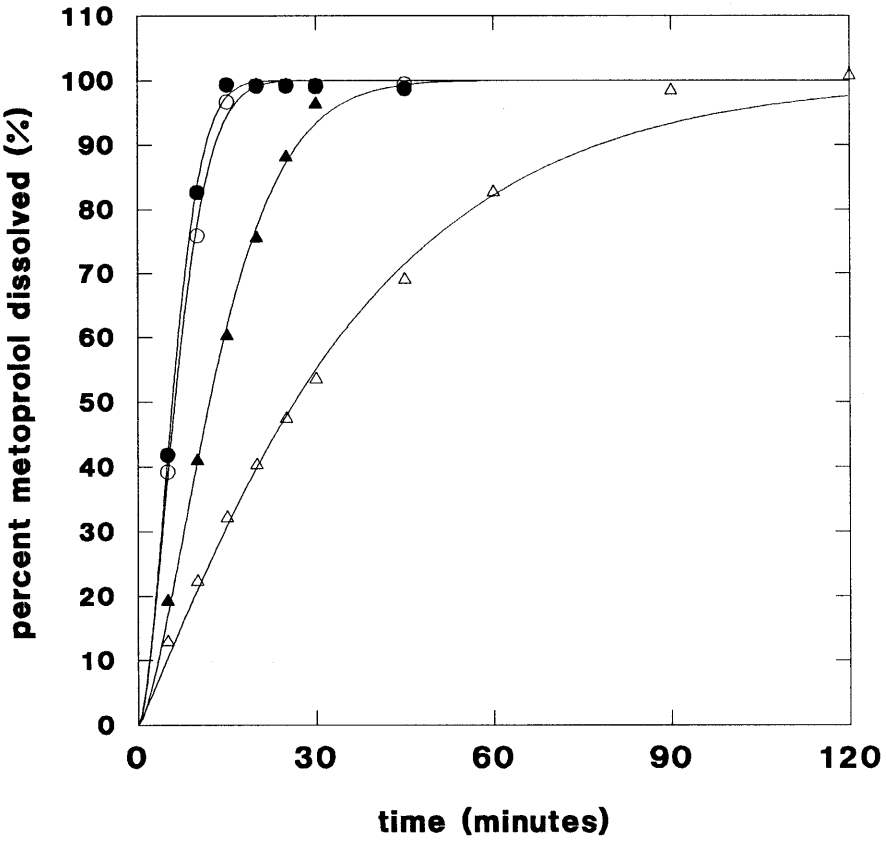

FIGURE 1. Mean (n = 6) dissolution profiles of Lopressor® (closed circle) and three UMAB formulations, fast (open circle), medium (closed triangle), and slow (open triangle). SE bars not shown since smaller than symbol. The Weilbull function using the mean τ and β parameters for each formulation is drawn.

cent dissolved at 60 and 90 minutes for Lopressor®, the fast test formula, and the medium test formula were assigned values of 100% for each sample.

Model-independent approaches can be further differentiated as ANOVA-based procedures, ratio test procedures, or pair-wise procedures. Two ANOVA-based procedures were evaluated: ANOVA on the percent dissolved at each time point and the level and shape approach (2). For the ANOVA testing of the percent dissolved data, one-way ANOVA plus Tukey's test for times 5–45 minutes were conducted. For 60 and 90 minute data, the one-sample t-test, which compared the percent dissolved of the slow formula against 100%, was conducted. Each of the "level" and "shape" portions of the level and shape approach were performed. Prior to analysis by the level and shape approach, the data were transformed in terms of first difference (2). These ANOVA methods used SYSTAT (SYSTAT, Inc., Evanston, IL).

Three types of ratio test procedures were performed: ratio tests of percent dissolved, ratio tests of area under the dissolution curve, and ratio tests of mean dissolution time. Each of these procedures compares the dissolution profile of two formulations at a particular time point. Ratio tests of percent dissolved were performed to give a 90% confidence interval for the mean ratio of percent dissolved. Similar procedures were followed for the ratio tests of area under the dissolution curve and ratio tests of mean dissolution time.

A third category of model-independent methods examined is denoted pair-wise procedures, which include the difference factor (3) (f_1), the similarity factor (1,3) (f_2), and two Indices of Rescigno (4) (ξ_1 and ξ_2). Like the ratio test procedures, these pair-wise procedures compare the dissolution profiles of a pair of products and can employ a 90% confidence interval approach.

Model-dependent Methods

Eight model-dependent approaches were used to compare metoprolol dissolution profiles. The model-dependent approaches included zero-order, first-order, Hixson-Crowell, Higuchi, quadratic, Weibull, Gompertz, and logistic models. The procedure to compare two dissolution profiles using a model-dependent approach follows and resembles the above ratio test procedures since a 90% confidence interval is ultimately constructed. For each of the two formulations being compared, the model under study was fitted to each individual dissolution profile using SYSTAT. From the mean ratio of the model parameter and the SE of the mean ratio, a 90% confidence interval was constructed.

RESULTS AND DISCUSSION

Model-independent Approaches

The result of the one-way ANOVA for each time point from 5–60 minutes was a p-value <0.001. The results of the one-sample t- test at 60 and 90 minutes were p-values of 0.389 and 0.560. While these results are informative, ANOVA may serve as a conservative method. The level and shape approach appeared to possess the same limitation as ANOVA of the percent dissolved at each time point, in that the level and shape approach addresses a question concerning the statistical sameness rather than pharmaceutical sameness. When dissolution data out to 30, 45, and 60 minutes were considered, the p-values for the "level" test statistic and the "shape" test statistic were always <0.0002. When dissolution out to 90 minutes was considered, the level and shape p-values were 0.467 and <0.0002, respectively.

Figure 2 shows the ratio of mean percent dissolved for fast versus Lopressor®, medium versus Lopressor®, and slow versus Lopressor®. Throughout the dissolution, the ratio of the percent metoprolol tartrate dissolved from the fast formulation was always within 90% of that from Lopressor®. During the first 10 minutes, the medium dissolving test formula was less than half of that of Lopressor®, but by 25 minutes it was about 90% of that from Lopressor® and by 45 minutes it was fully dissolved like Lopressor®. For slow ver-

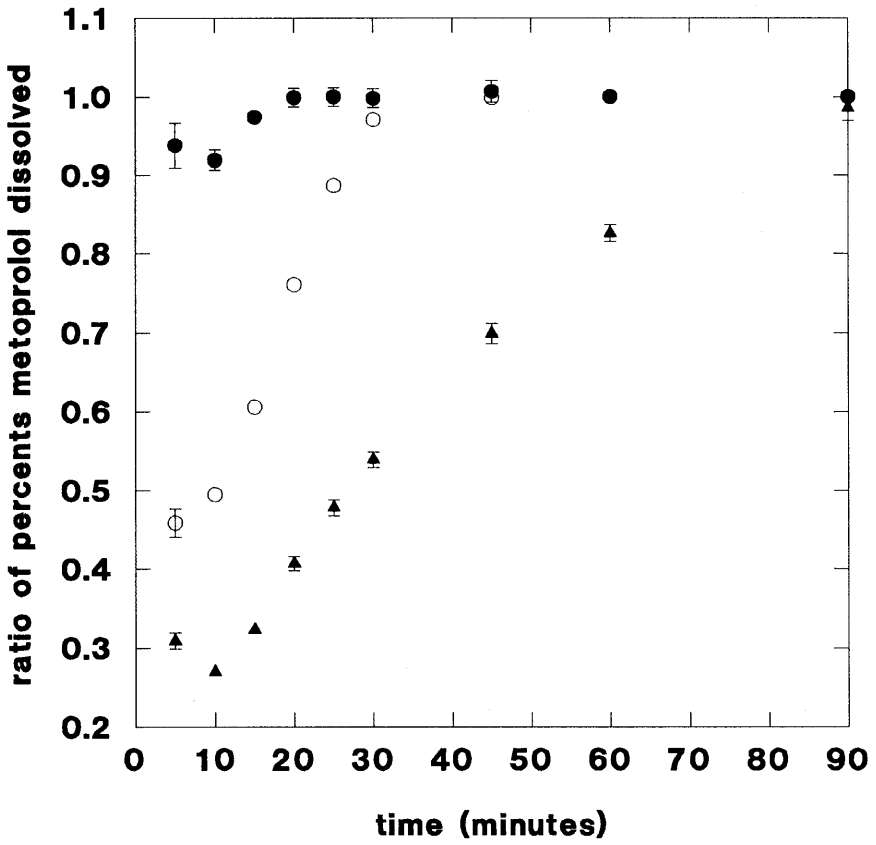

FIGURE 2. Ratio of mean percent dissolved for fast (closed circle) versus Lopressor®, medium versus Lopressor® (open circle), and slow versus Lopressor® (closed triangle). Error bars denote SE from n = 6.

sus Lopressor®, the ratio was below 0.8 for the first 45 minutes; only until 60 minutes did the ratio reach a value greater than 0.8. The 90% confidence intervals for the mean ratio of percents dissolved were about twice as wide as the SE bars in Figure 1.

Figure 3 illustrates the ratio of areas under the dissolution curve for fast versus Lopressor®, medium versus Lopressor®, and slow versus Lopressor® up until 30, 60, and 90 minutes. The ratio of the areas from the fast formulation was always within 90% of that from Lopressor®. Over the first 30 minutes, the medium dissolving test formula gave a value of about 0.7 (ie, $1600 \pm 18\%$ dissolved·minutes vs. $2358 \pm 10\%$ dissolved·minutes) and still was not 100% dissolved. For slow formulation versus Lopressor®, the ratio started very low, never reached a value greater than 0.7 by 90 minutes, and was always below the 0.8 specification mentioned above. For slow versus Lopressor® at 90 minutes, the 90% confidence interval for the mean ratio of areas interval was 0.662–0.702.

Figure 4 plots the ratio of average mean dissolution times for fast versus Lopressor®, medium versus Lopressor®, and slow versus Lopressor®. As shown by fast versus Lopressor® and medium versus Lopressor®, the ratio of mean dissolution times changed little as additional dissolution time samples near 100% dissolved for both products were considered. The ratio of the mean dissolution time from the fast formulation versus that of Lopressor® was always nearly 1.0 (eg, $7.2 \pm$

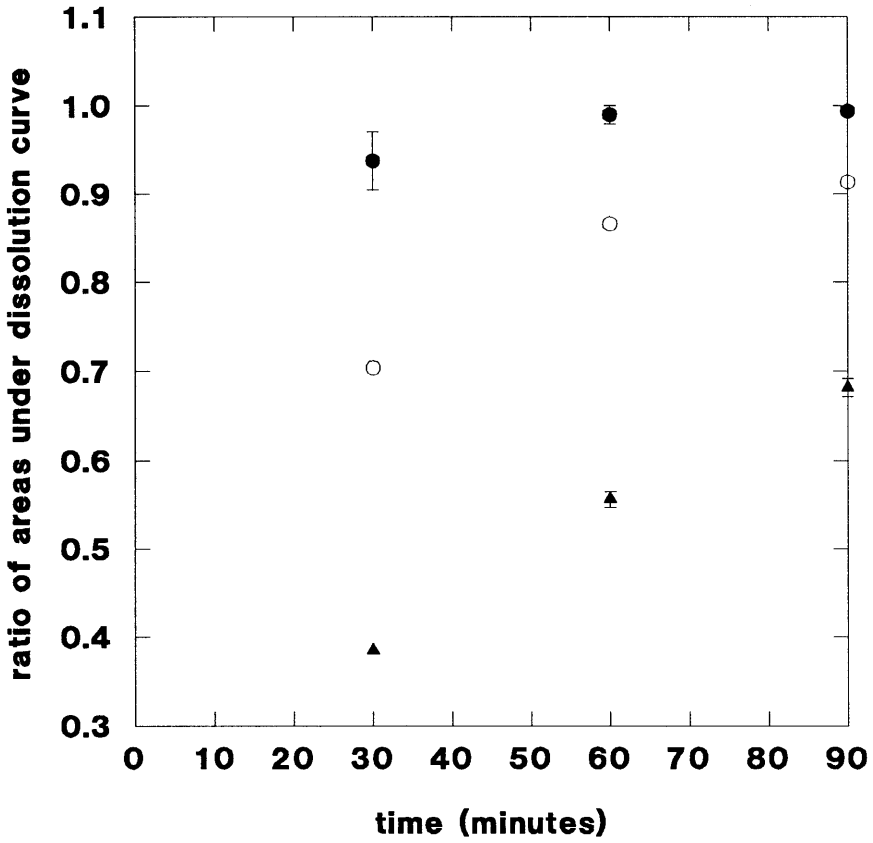

FIGURE 3. Ratio of mean areas under the dissolution curve for fast (closed circle) versus Lopressor®, medium versus Lopressor® (open circle), and slow versus Lopressor® (closed triangle). Error bars denote SE from n = 6.

0.5 minutes vs. 6.7 ± 0.2 minutes at 20 minutes). The medium dissolving test formula took about twice as long as Lopressor® to dissolve. For slow versus Lopressor®, the ratio was almost five, and the 90% confidence interval was 4.6–5.0.

Results of several pair-wise procedures —the difference factor, the similarity factor, and two Indices of Rescigno—are reported here. Table 1 lists the mean (±SE) values of f_1, f_2, ξ_1, and ξ_2, respectively, for fast versus Lopressor®, medium versus Lopressor®, and slow versus Lopressor®, up until 90 minutes. For fast versus Lopressor®, medium versus Lopressor®, and slow versus Lopressor®, f_1 was about 3, 20, and 50. f_2 was about 70, 30, and 15. The ξ_1 values for fast versus Lopressor®, medium versus Lopressor®, and slow versus Lopressor® were about 0.01, 0.1, and 0.3. The ξ_2 values were roughly the same as ξ_1, but were larger.

Model-dependent Approaches

Several of the eight models were successfully fitted to each dissolution profile. The zero-order model did not provide an adequate fit. The Gompertz and logistic models, which have three parameters, could not accommodate the Lopressor® data because of the insufficient number of samples for Lopressor®.

Results from Weibull, Hixson-Crowell, and first order fits are highlighted here. Table 2 lists the mean fitted parameters for these models. As dissolution was slowed across the formulations, Weibull τ grew larger, which is

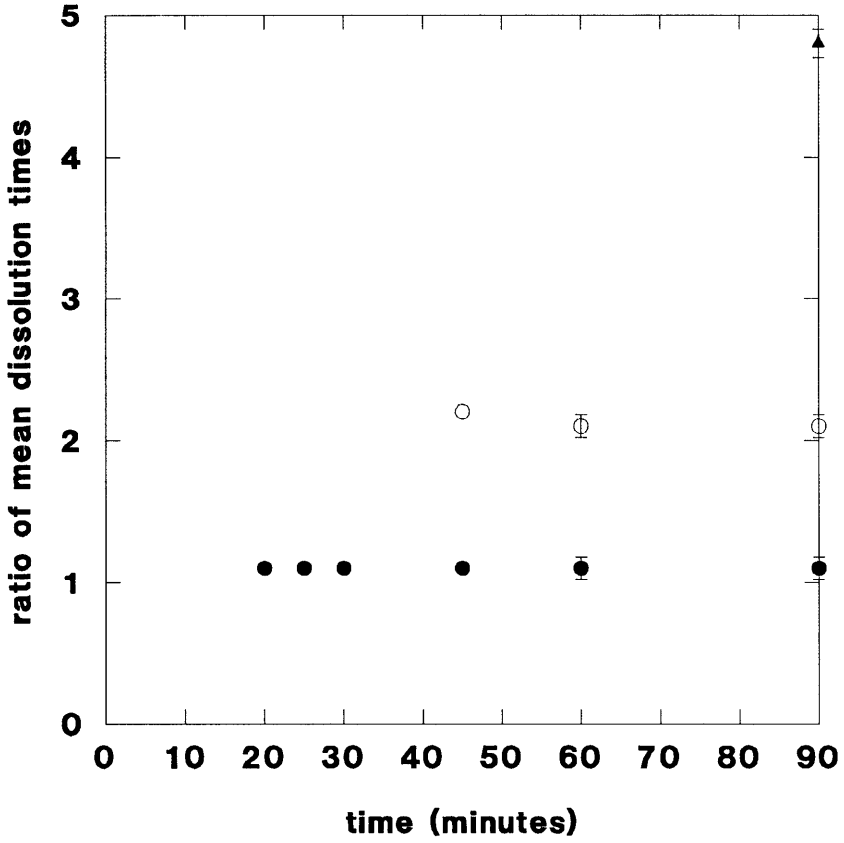

FIGURE 4. Ratio of average mean dissolution times for fast (closed circle) versus Lopressor®, medium versus Lopressor® (open circle), and slow versus Lopressor® (closed triangle). Error bars denote SE from n = 6.

in agreement with the interpretation that this parameter reflects the scale of time for the process. Weibull β, a shape factor, decreased across the formulations and indicates that the slower formulations possessed lesser sigmoid shape. Hixson-Crowell *k* and first-order *k* decreased by similar extents. In Table 3, the mean ratio of each parameter for fast versus Lopressor®, medium versus Lopressor®, and slow versus Lopressor® is given. The ratio of the Weibull β was always less than one and reiterates that each test formula has a less "S"-shape compared to Lopressor®. Ratios for Weibull τ, Hixson-Crowell *k*, and first-order *k* each agree semiquantitatively with each other and with results from other model-independent methods, that the dissolution rate from the fast, medium, and

TABLE 1
Mean Value (SE) of f_1, f_2, ξ_1, and ξ_2

Metric	Fast versus Lopressor	Medium versus Lopressor	Slow versus Lopressor
f_1	2.11 (0.34)	17.42 (0.49)	44.34 (0.63)
f_2	76.9 (2.8)	32.6 (0.5)	17.7 (0.3)
ξ_1	0.0064 (0.0011)	0.0443 (0.0014)	0.1917 (0.0045)
ξ_2	0.0111 (0.0016)	0.0865 (0.0022)	0.2229 (0.0046)

TABLE 2
Mean Model-dependent Parameters (SE) of Metoprolol Tartrate Dissolution

Product	Last Dissolution Time Point	Weibull τ (Minutes)	Weibull β	Hixson-Crowell k ($mg^{1/3}$/minutes)	First-Order k ($minutes^{-1}$)
Lopressor	15 minutes	7.14 (0.07)	1.75 (0.02)	0.189 (0.002)	0.150 (0.002)
Fast	20 minutes	7.81 (0.16)	1.62 (0.03)	0.172 (0.004)	0.139 (0.003)
Medium	45 minutes	15.4 (0.2)	1.49 (0.02)	0.0852 (0.0015)	0.0669 (0.0013)
Slow	90 minutes	36.7 (1.0)	1.11 (0.02)	0.0353 (0.0010)	0.0269 (0.0008)

slow formulations are about equal to, half, and one-fifth of that of the reference. The 90% confidence intervals are shown in Table 3.

OTHER COMMENTS

It appears that metric limits for the profile similarity of this metoprolol tartrate tablet formulation may be relatively wide, assuming the USP method serves as a surrogate for bioequivalence. Two issues arise from this observation. First, these results suggest that the 50–100 acceptance criteria (1) for f_2 appears conservative. For slow versus Lopressor®, a value of 17.7 still resulted in tablets which were bioequivalent. While a conservative approach would require a bioequivalence study (1), a liberal approach would widen the acceptance criteria for f_2 to 17.7–100. In the event that a liberal approach were taken and the criteria for profile similarity were widened, a second issue arises: Can this wider acceptance criteria be applied to other metoprolol tartrate tablet formulations or even other drugs? A conservative approach would not allow extrapolation of dissolution specifications of this particular metoprolol tartrate tablet formulation to any other products. A liberal approach would allow the application of the wider specification to other immediate release metoprolol tartrate tablet formulations. An increasingly more liberal approach would allow the application of the wider specification to other formulations containing drugs which are similar to metoprolol tartrate in their biopharmaceutical properties.

CONCLUSIONS

The main objective of this work was to apply several profile comparison approaches to one dissolution data set in order to quantify each method's metric for comparing dissolution profiles. In spite of the need to compare dissolution profiles, methods to compare dissolution profiles are not well developed. This work was conducted with the intent to investigate several methods and to gain familiarity with the numerical values of those methods. It is concluded that the ratio test procedures, the pair-wise procedures, and several of the model-dependent approaches yielded numerical results which can possibly serve as objective and quantitative metrics for compar-

TABLE 3
Mean (SE) Values of Ratios of Model-dependent Dissolution Parameters

Parameter	Ratio of Fast to Lopressor	Ratio of Medium to Lopressor	Ratio of Slow to Lopressor	90% Confidence Interval of Ratio of Slow to Lopressor
Weibull τ	1.09 (0.02)	2.16 (0.04)	5.14 (0.15)	4.82–5.46
Weibull β	0.926 (0.020)	0.851 (0.015)	0.634 (0.014)	0.604–0.663
Hixson-Crowell k	0.910 (0.02)	0.451 (0.009)	0.187 (0.006)	0.175–0.198
First-order k	0.927 (0.02)	0.446 (0.011)	0.179 (0.006)	0.168–0.191

ing entire dissolution profiles of the four metoprolol tartrate formulations.

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