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COMMUNICATION

Statistical Evaluation of In Vitro Dissolution of Different Brands of Ciprofloxacin Hydrochloride Tablets and Capsules

Yeqiu Tang* and Kesu Gan

Department of Pharmacy, Chang Shu No. 1 People's Hospital, Chang Shu, Jiangsu, The People's Republic of China

ABSTRACT

The in vitro dissolution of ciprofloxacin from commercially available tablets and capsules in China was studied using the USP apparatus I to compare the product performance from nine different manufacturers. Cumulative release grater than 75% was obtained from all of the products tested within 45 min. However, statistically significant differences were found between some of the products when in vitro data were analyzed using the Weibull function, similarity factor (f_2), and multivariate analysis of variances.

INTRODUCTION

Ciprofloxacin is a well-known synthetic broad-spectrum antibacterial agent in the quinolone class. It is practically insoluble in aqueous medium at neutral pH. However, the permeation of ciprofloxacin through the gastrointestinal membrane is expected to be rapid and complete because of its favorable lipophilicity. According to the biopharmaceutic drug classification scheme, it is a Case II drug, i.e., low solubility–high permeability (1). Drugs in this class can be expected to have variable absorption because of the many formulation and in vivo variables that can effect the dissolution profile (1). Therefore, dissolution of ciprofloxacin oral products is one of the parameters critical to the product quality and in vivo performance.

The objective of the present study was to compare and evaluate in vitro product performance of commer-

*To whom correspondence should be addressed.

cially available ciprofloxacin tablets and capsules from nine manufacturers in China using USP standardized dissolution test.

MATERIALS AND METHODS

Materials and Equipment

The following products of ciprofloxacin were tested in the study: tablet A, lot no. 950804 (manufacturer A), tablet B, lot no. 950515 (manufacturer B), tablet C, lot no. G96604 (manufacturer C), tablet D, lot no. 960201 (manufacturer D), tablet E, lot no. 960106 (manufacturer E), capsule F, lot no. 950701 (manufacturer F), capsyle G, lot no. 950428 (manufacturer G), capsule H, lot no. 950912 (manufacturer H), capsule I, lot no. 950312 (manufacturer I). The potencies of the tested dosage forms were 250 mg for tablets and 200 mg for capsules. All other chemicals and reagents were analytical reagent grades and used as received. A ZRS4 dissolution tester (Electronic Factory of Tianjin University, Tianjin, China) and a UV-VIS spectrophotometer (WFZ-34, Tianjin Optics Instruments, Tianjin, China) were used in dissolution tests.

In Vitro Dissolution Test

The in vitro dissolution tests were performed using the USP apparatus I (basket method) with six replicates. The dissolution medium was 1000 ml of 0.1 N HCl maintained at 37 ± 0.5°C. The basket rotation speed was kept at 100 rpm. In all experiments, 5 ml of dissolution sample was withdrawn at 3, 7, 12, 20, 30, 45, and 60 min, and replaced with an equal volume of the fresh medium to maintain a constant total volume. Samples were passed through a filter (0.8 μm) and assayed by UV spectrophotometry at 277 nm. Cumulative percentages of the drug released from the dosage forms were calculated. The potency of each formulation and 24-hr stability of ciprofloxacin in the dissolution medium at room temperature were confirmed prior to the start of the dissolution test.

Data Analysis

Experimental data were analyzed using four different methods: (*a*) USP standard, i.e., >75% release at 45 min; (*b*) analysis of variance (ANOVA) tests on dissolution parameters derived from curve fitting to Weibull function, i.e., mean dissolution time (T_d) and times required for 50 and 80% release (T_{50} and T_{80}); (*c*) analysis using similarity factor (f_2) defined in FDA SUPAC guidelines for immediate release solid oral dosage forms; (*d*) comparison of the complete dissolution profiles using multivariate ANOVA (MANOVA). Data analyses using ANOVA were carried out using JMP 3.1 (SAS Institute Inc., Cary, NC).

RESULTS AND DISCUSSION

In Vitro Dissolution

The in vitro dissolution profiles of ciprofloxacin tablet and capsule products from different manufacturers are presented in Figs. 1 and 2. Because cumulative release of all products reached plateau at 30 min, data at 45 and 60 min are not shown. Each data point represents an average of six measurements for each formulation. It was evident that all products tested meet the general dissolution specifications of USP (2), i.e., dissolution greater than 75% is within 45 min. However, complete drug release from tablet D was not obtained.

Statistical Analysis

To further compare the in vitro dissolution performance among different products, two products with the fastest release rates were selected as reference standards for two types of dosage forms, i.e., tablet A and capsule H.

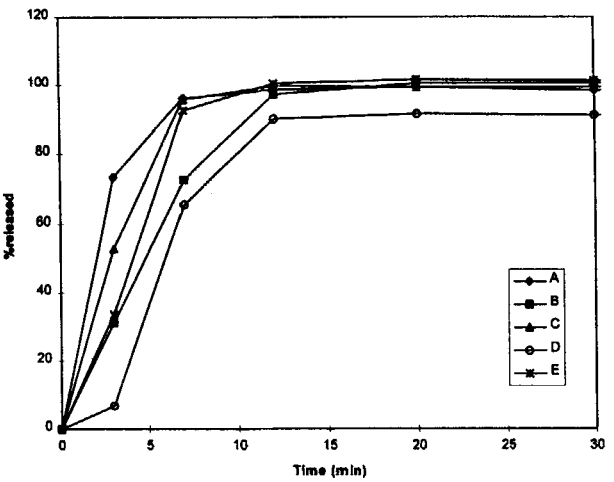

Figure 1. Average in vitro dissolution profiles of ciprofloxacin hydrochloride tablets from different manufacturers (n = 6)

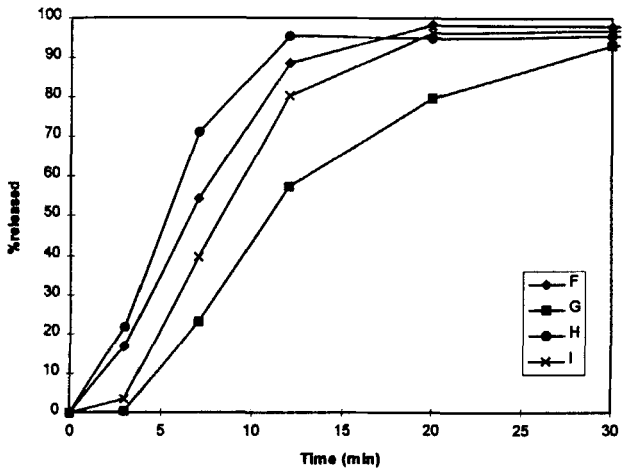

Figure 2. Average in vitro dissolution profiles of ciprofloxacin hydrochloride capsules from different manufacturers ($n = 6$)

Dissolution Parameters Based on Weibull Distribution Function

It has been reported that the in vitro dissolution profiles from tablets or capsules can be characterized by an empirical equation, the Weibull function (3):

$$Q(t) = 1 - e^{-(t\beta/\alpha)} \quad (1)$$

where $Q(t)$ is the amount dissolved at time t. The scale factor α and shape factor β are adjustable parameters. The results of fitting individual tablet and capsule data to Eq. (1) are listed in Table 1. Dissolution parameters, T_d, T_{50}, and T_{80} were calculated based on Eq. (1). Analysis of variance indicated significant differences in all three parameters among tablet ($p < 0.01$) and capsule products ($p < 0.01$).

Similarity Factor

According to FDA guidelines on scale-up and postapproval changes (SUPAC) for immediate release solid dosage forms (4), dissolution profiles can be compared using the following equation that defines a similarity factor f_2:

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \cdot 100\right\} \quad (2)$$

where R_t and T_t are the percent dissolved at each time point. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. The f_2 values for each of the products tested in this study are given in Table 2. It was found that release profiles of tablets B–E were different from that of the reference tablet A, although the f_2 value of tablet C was near the lower limit of the similarity range. Capsules F and I showed in vitro dissolution performance similar to the reference capsule H, and the f_2 value of capsule G indicated a different dissolution profile.

Comparison of Dissolution Profiles Using MANOVA

Because cumulative release data at each time point are intercorrelated, MANOVA was used to compare all of the dissolution profiles of different tablet and capsule products. Wilks' lambda test indicated statistically significant differences among tablets A–E ($p < 0.0001$) and capsules F–I ($p < 0.0001$). Further evaluation of

Table 1

Results of Data Analysis Using Weibull Function

Product	β	T_d	T_{50}	T_{80}
A	1.05 ± 0.56	2.19 ± 0.1.16	1.55 ± 0.94	3.58 ± 1.46
B	1.17 ± 0.21	5.88 ± 0.78	4.26 ± 0.75	8.91 ± 1.01
C	1.15 ± 0.33	3.17 ± 0.35	2.27 ± 0.41	4.97 ± 0.36
D	1.56 ± 0.38	10.73 ± 1.34	8.35 ± 0.98	14.94 ± 2.42
E	1.28 ± 0.34	4.73 ± 1.20	3.56 ± 1.15	6.90 ± 1.09
F	1.24 ± 0.12	8.91 ± 0.64	6.62 ± 0.56	13.13 ± 0.90
G	2.60 ± 0.28	18.62 ± 2.47	16.15 ± 2.23	22.39 ± 2.85
H	0.92 ± 0.43	7.08 ± 3.76	4.87 ± 3.40	11.93 ± 3.78
I	1.70 ± 0.41	14.18 ± 3.32	11.66 ± 3.19	19.25 ± 3.08

Table 2

In Vitro Dissolution Similarity Factors (f_2) of Commercially Available Ciprofloxacin Hydrochloride Tablets and Capsules

Tablet	f_2	Capsule	f_2
A	100.0	F	65.7
B	30.7	G	42.2
C	49.1	H	100.0
D	21.5	I	52.4
E	34.7		

the dissolution data of individual tablet product against reference tablet A demonstrated that tablets B ($p = 0.0002$), D ($p < 0.0001$), and E ($p = 0.0069$) were significantly different from tablet A, whereas the difference between tablet C and the reference was insignificant ($p = 0.0769$). Dissolution curves of capsule G ($p = 0.001$) and I ($p = 0.0037$) were also found to be different from that of reference capsule H. However, capsule F did not show significantly different dissolution profile from capsule H ($p = 0.1930$). The same conclusions were derived in all cases using other tests, such as Pillai's Trace, Hotelling–Lawley, and Roy's max root tests.

In most cases, the results from MANOVA were in accordance with those obtained using similarity factor, with the exception of capsule I. The discrepancy may be attributed to the fact that all individual data were included in MANOVA analysis, but only the average data were used for determination of f_2 values.

CONCLUSIONS

The results in this study indicated significant differences in in vitro dissolution of ciprofloxacin among different commercial tablet and capsule products in China. The potential impact of these differences on the in vivo bioavailability of the products may warrant further investigation.

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