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Temperature, pH and agitation rate as dissolution test discriminators of zofenopril calcium tablets

RUBEN LOZANO,* JOHN M. JOSEPH and BERRY J. KLINE

Department of Analytical Research & Development, Bristol-Myers Squibb Pharmaceutical Research Institute, 1 Squibb Drive, New Brunswick, NJ 08903, USA

Abstract: Comparative *in vitro* dissolution studies were performed on several tablet batches of zofenopril calcium, an ACE inhibitor, to determine if they could be differentiated on the basis of their release rates. The samples included six batches produced at Site 1 and one batch produced at Site 2. Using regular dissolution conditions (USP paddle method at a 50-rpm agitation speed in phosphate buffer, pH 7.5, at 37°C), release rates of all the tablet batches were similar. By independently altering one of the dissolution test parameters, either a lower pH or a slower agitation rate, discrimination between the Site 1 and Site 2 tablets was enhanced. Discrimination was only slightly enhanced when a lower dissolution medium temperature was used. Tablets made from different polymorphs of zofenopril calcium could not be differentiated by their dissolution profiles, even with the more discriminating conditions. The dissolution profiles of certain other zofenopril calcium tablets (including film-coated vs uncoated tablets, and tablets made with micronized vs unmicronized drug particles) were indistinguishable using a 50-rpm agitation rate, but they could be clearly differentiated using a 40-rpm agitation rate.

Keywords: *Zofenopril calcium; dissolution; tablet discrimination; paddle agitation rate.*

Introduction

Zofenopril calcium (SQ-26991), an orally administered ester prodrug (Fig. 1) which undergoes *in vivo* hydrolysis to an active inhibitor of angiotensin converting enzyme [1], has been under development as an antihypertensive agent in solid dosage formulations. The regular dissolution assay for zofenopril calcium tablet formulations is performed in simulated intestinal fluid without enzyme (0.05 M potassium phosphate buffer, pH 7.5) at 37°C using the USP paddle method at a rotation speed of 50 rpm. In a comparative analysis of 30 mg potency tablets produced according to the same formulation at two different manufacturing sites, Site 1 and Site 2, it was found that the release rates of the tablet batches were similar. The release rate of Site 1 tablets was consistently slower than that of Site 2 tablets, although the difference between the rates was slight.

Variable dissolution test parameters such as the type of apparatus, the type and rate of agitation, and the volume, composition and temperature of the dissolution fluid have all been shown to influence the *in vitro* rate of drug release from pharmaceutical dosage forms [2]. A study of the effects of agitation rate, particle size, and dissolution fluid pH on

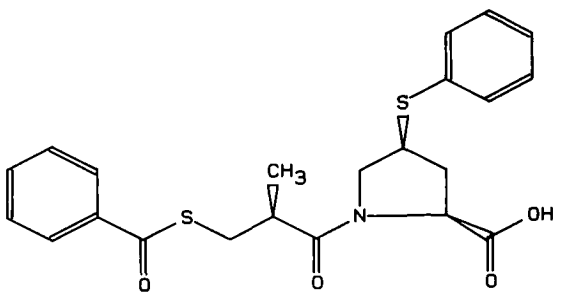

Figure 1
Chemical structure of zofenopril.

* Author to whom correspondence should be addressed.

the *in vitro* release of acetylsalicylic acid from hard gelatin capsules led to the conclusion that, even for formulations containing a drug with pH-dependent solubility, the agitation speed had the greatest influence on the dissolution rate [3]. More recently, the *in vitro* dissolution rate of ampicillin and amoxycillin embonate salts was investigated as a function of the medium pH]4].

The objective of our study was to determine whether the dissolution rate of zofenopril calcium in either of these two tablet batches was particularly sensitive to slight changes in any of the dissolution test conditions. If so, altering that particular test condition might effect greater discrimination between the two batches of tablets. Thus, the following experimental parameters were varied independently: medium temperature (32 vs 37°C), medium pH (7.0 vs 7.5 vs 7.8), and paddle rotation rate (40 vs 50 rpm). After establishing a more discriminating test condition, its ability to differentiate between several batches of tablets produced at the same site was then examined.

The dissolution test was also investigated as a possible discriminator of the physical state of the bulk drug in the tablet formulation. Since zofenopril calcium exhibits polymorphism, dissolution rates were obtained for tablets prepared with either of two polymorph types, A or B. Finally, the ability of the dissolution test to discriminate between tablets containing different particle sizes of bulk zofenopril calcium (i.e. micronized vs unmicronized bulk drug), and also between film-coated and uncoated tablets of zofenopril calcium was examined.

Experimental

Zofenopril calcium tablets with 30 mg and 60 mg potencies were produced at two Bristol-Myers Squibb manufacturing sites, designated as Site 1 and Site 2. USP Apparatus II (paddle method) was used to conduct the dissolution tests in a VanderKamp 600 six-spindle dissolution tester (VanKel Industries, Edison, NJ). The dissolution medium consisted of 1000 ml of 0.05 M potassium phosphate buffer, adjusted to a pH of either 7.0, 7.5 or 7.8 with 2.5 N sodium hydroxide solution. The medium was maintained at either 32 or 37°C. The paddle rotation speed was set at either 40 or 50 rpm, with instrument variation at about ±1 rpm. Samples were withdrawn at time intervals of 10, 20, 30, 60 and 90 min from test initiation. The samples were immediately filtered throughout Gelman Acrodisc filter units with 1.2 μm pore size. The filtered samples were assayed for zofenopril calcium by UV spectrophotometry at 247 nm using a UV–vis spectrophotometer (Gilford Systems Model Response, Ciba Corning Diagnostics, Oberlin, OH). The dissolution results represent means from tests with $n \geq 6$.

Results and Discussion

Dissolution profiles for Site 1 and Site 2 batches of zofenopril calcium tablets obtained at two different medium temperatures (32°C vs 37°C), with constant pH (7.5) and paddle rotation speed (50 rpm), are shown in Fig. 2. At 37°C, Site 1 tablets had a slightly slower release rate than Site 2 tablets. However, at 32°C, the difference in release rates between the two batches was somewhat enhanced.

Dissolution profiles for Site 1 and Site 2 tablets were obtained in phosphate buffer media of three different pH values (7.0, 7.5 or 7.8), with constant paddle speed (50 rpm) and temperature (37°C). The release rate of Site 1 tablets was similar in either pH 7.5 or 7.8, but noticeably slower in pH 7.0. The release rates of Site 2 tablets were virtually identical in all three media. In either pH 7.5 or 7.8 media, the dissolution rates of Site 1 tablets were nearly identical to those of Site 2 tablets (Fig. 3). In pH 7.0 media, the two batches were more clearly discriminated (Fig. 3).

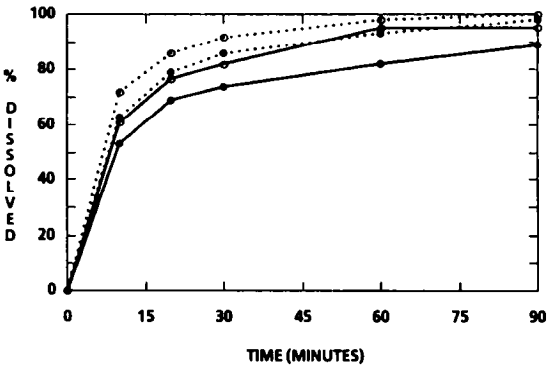

Figure 2
Effect of medium temperature on dissolution rate of zofenopril calcium 30 mg tablets. Site 1 tablets at 32°C (●—●): standard error of mean (SE) <2.4%; Site 2 tablets at 32°C (○—○): SE <1.5%; Site 1 tablets at 37°C (●····●): SE <0.6%; Site 2 tablets at 37°C (○····○): SE <0.9%. Dissolution medium pH 7.5. Paddle rotation speed = 50 rpm.

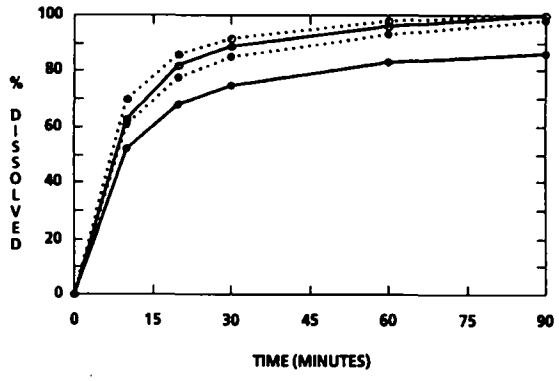

Figure 3
Effect of medium pH (7.0 vs 7.5) on dissolution rate of zofenopril calcium 30 mg tablets. Site 1 tablets at pH 7.0 (●—●): SE <3.4%; Site 2 tablets at pH 7.0 (○—○): SE <0.8%; Site 1 tablets at pH 7.5 (●····●): SE <0.6%; Site 2 tablets at pH 7.5 (○····○): SE <0.9%. Dissolution medium temperature = 37°C. Paddle rotation speed = 50 rpm.

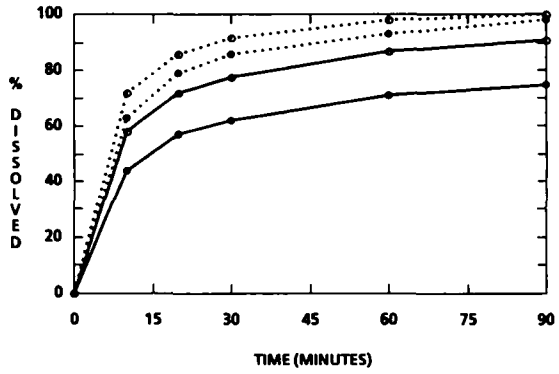

Figure 4
Effect of paddle rotation speed on dissolution rate of zofenopril calcium 30 mg tablets. Site 1 tablets at 40 rpm (●—●): SE <4.6%; Site 2 tablets at 40 rpm (○—○): SE <1.9%; Site 1 tablets at 50 rpm (●····●): SE <0.6%; Site 2 tablets at 50 rpm (○····○): SE <0.9%. Dissolution medium pH 7.5; temperature = 37°C.

Dissolution profiles for Site 1 and Site 2 tablet batches obtained at two different paddle rotation speeds (40 vs 50 rpm), with constant temperature (37°C) and pH (7.5), are shown in Fig. 4. At 50 rpm, Site 1 tablets had a slightly slower release rate than Site 2 tablets. However, at 40 rpm, the difference in release rates between the two batches was enhanced.

Utilizing the more discriminating test condition of a 40 rpm paddle rotation speed, additional observations on the dissolution characteristics of zofenopril calcium tablets were made. Figure 5 shows dissolution profiles obtained using a 40 rpm rotation speed for six batches of zofenopril calcium tablets produced at Site 1, in comparison to the Site 2 tablet

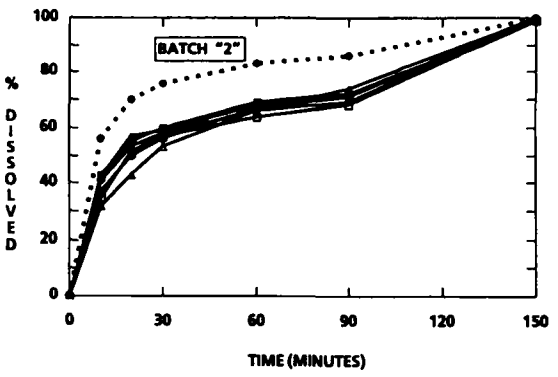

Figure 5
Dissolution profiles of zofenopril calcium 30 mg tablets using a paddle rotation speed of 40 rpm, increased to 100 rpm after 90 min. Site 2 tablets (●····●): SE <0.9%; the remaining solid-line graphs represent six batches from Site 1: SE <4.6%. Dissolution medium pH 7.5; temperature = 37°C.

batch. As an experimental control, the paddle speed was increased from 40 to 100 rpm at the 90 min timepoint, to ensure complete release (100% dissolved) of zofenopril calcium from the tablet matrix. The dissolution profiles of the six tablet batches from Site 1 were virtually indistinguishable from each other, indicating good batch-to-batch uniformity, and were discriminated completely from the profile of the Site 2 tablet batch. With respect to comparative age of the six Site 1 batches, one batch was a 2-year-old lot (stored at ~25°C), whereas the other five batches were relatively new lots. Therefore, age differences among these particular batches did not appear to influence the drug release rates.

The effect of the polymorphic nature of zofenopril calcium on its release rate from tablet formulations was also examined. The dissolution rate of drug compounds that exhibit polymorphism may depend upon the characteristics of the specific polymorphs used in the formulation [2]. Distinct dissolution rates for two different polymorphs of methylprednisolone have been demonstrated in early studies, and furthermore, those differences in dissolution rates were non-existent at higher agitation speeds [5, 6]. Similarly, distinct differences in dissolution rates and bioavailability between different polymorphic forms of drugs have been demonstrated for sulphathiazole [7] and phenylbutazone [8]. From our studies, dissolution profiles for two batches of 60 mg tablets prepared with either of two zofenopril calcium polymorphs, A or B, are demonstrated in Fig. 6. The dissolution tests were conducted

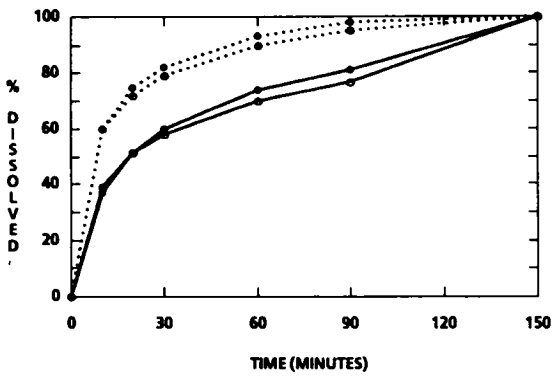

Figure 6
Dissolution profiles of zofenopril calcium tablets prepared with two different polymorphs. Polymorph-A tablets at 40 rpm (●—●): SE <1.5%; Polymorph-B tablets at 40 rpm (○—○): SE <0.9%; Polymorph-A tablets at 50 rpm (●···●): SE <1.4%; Polymorph-B tablets at 50 rpm (○···○): SE <1.8%. Paddle rotation speed was increased to 100 rpm after 90 min. Dissolution medium pH 7.5; temperature = 37°C.

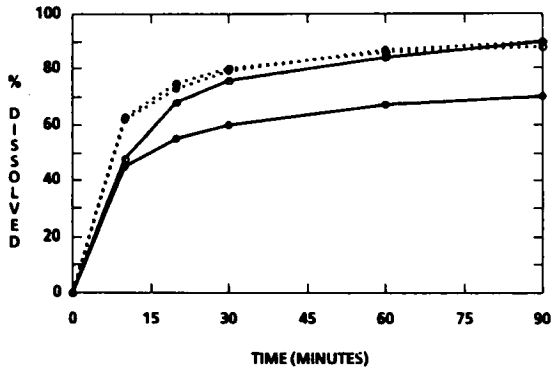

Figure 7
Dissolution profiles of film-coated vs uncoated zofenopril calcium 60 mg tablets. Film-coated tablets at 40 rpm (●—●): SE <2.0%; uncoated tablets at 40 rpm (○—○): SE <1.8%; film-coated tablets at 50 rpm (●···●): SE <1.0%; uncoated tablets at 50 rpm (○···○): SE <1.6%. Dissolution medium pH 7.5; temperature = 37°C.

with paddle speeds at 40 and 50 rpm. (In the 40 rpm tests, the agitation speed was increased to 100 rpm after 90 min, in order to demonstrate complete drug release.) At either agitation rate, the dissolution profiles of the two tablet batches were not significantly different (paired *t*-test $P > 0.05$). Therefore, zofenopril calcium tablets prepared with either of two different polymorphs could not be differentiated on the basis of their dissolution rates, even with the more discriminating 40 rpm agitation speed.

Dissolution profiles for a corresponding pair of film-coated and uncoated tablet batches of zofenopril calcium 60 mg are shown in Fig. 7. The dissolution tests were conducted with paddle speeds at 40 and 50 rpm. The two batches were indistinguishable using the agitation rate of 50 rpm. However, the batches were clearly differentiated using a 40 rpm agitation speed, as dissolution of the film-coated tablets occurred substantially slower. In this case, the difference in dissolution rates between the two types of tablets might be due mostly to the effects of agitation speed upon filmcoat dissolution and tablet disintegration, rather than effects upon the drug itself.

The effects of paddle agitation rate and drug particle size on dissolution were examined. Higher dissolution rates are usually obtained by reducing drug particle size, as the drug surface area exposed to the dissolution medium effectively increases with decreasing particle size [2]. Dissolution profiles for a pair of zofenopril calcium 60 mg tablet batches which differ in the particle size of the bulk drug are shown in Fig. 8, obtained with paddle speeds at 40 and 50 rpm. One tablet batch was produced with micronized drug particles, and the other batch was produced with unmicronized (milled) drug. The two batches were indistinguishable using the agitation rate of 50 rpm. However, using the 40 rpm agitation rate, the dissolution rate of the tablets containing unmicronized drug was slower than that of the batch containing micronized drug. Therefore, utilization of the slower paddle rate greatly enhanced discrimination between these two types of tablets.

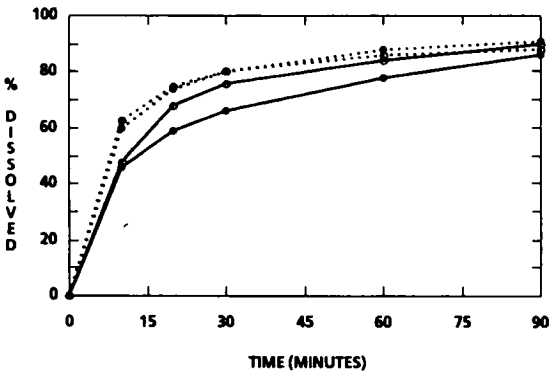

Figure 8
Dissolution profiles of zofenopril calcium 60 mg tablets produced with micronized vs unmicronized drug particles. Unmicronized drug tablets at 40 rpm (●—●): SE <1.8%; micronized-drug tablets at 40 rpm (○—○): SE <1.8%; unmicronized drug tablets at 50 rpm (●···●): SE <1.0%; micronized drug tablets at 50 rpm (○···○): SE <1.6%. Dissolution medium pH 7.5; temperature = 37°C.

Conclusions

Discrimination between batches of zofenopril calcium tablets produced at two different sites, as measured by their comparative *in vitro* dissolution rates, was enhanced by independently changing any of the following dissolution test parameters, applying relatively slight variations: a lower medium temperature (from 37 to 32°C); a lower medium pH (from 7.5 to 7.0); or a slower paddle rotation rate (from 50 to 40 rpm). Thus, the pH and temperature of the dissolution medium, and the paddle agitation rate are all critical factors for the *in vitro* release rate of zofenopril calcium from particular tablet formulations. Utilization of an atypical 40 rpm agitation rate demonstrated greater discriminatory power than did the more commonly used 50 rpm rate.

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