

In Vitro Dissolution Profiles of Two Diltiazem Tablet Formulations and a Compounded Capsule Formulation: A Comparative Study

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ABSTRACT

The dissolution test is usually employed to evaluate the performance of drug products. In this study, we compared the in vitro dissolution profiles of two diltiazem hydrochloride tablet formulations with that of a diltiazem hydrochloride compounded capsule formulation. Other characteristics investigated were average weight, drug content, disintegration, and uniformity of dosage units according to the *USP* monograph. The paddle apparatus was set at 75 rpm in 900 mL of water at 37.0 ± 0.1 °C. Samples of 10 mL were withdrawn at 15, 30, 60, 120, 180, and 210 min without replacement and immediately filtered with 0.45- μ m PVDF syringe filters. The samples were then analyzed employing a spectrophotometer at 237 nm. The similarity (f_2) and difference (f_1) factors were calculated for dissolution profile comparison. The drug contents of the reference, generic, and compounded products were 100.01%, 93.17%, and 98.48%, respectively. All of the products showed suitable acceptance values for drug content uniformity (3.16, 8.37, and 4.76 for reference drug, generic drug, and compounded capsule, respectively). The generic drug formulation showed a calculated f_2 value between 50 and 100 and an f_1 value less than 15. It was not possible to calculate the f_1 and f_2 values for the compounded capsules because they showed a drug release greater than 85% in 15 min. The generic and reference drugs were similar in relation to all tests. Furthermore, the generic and reference drug dissolution profiles were similar. The compounded capsules, which readily released the active ingredient, were not adequate only in the dissolution test. Further studies are necessary to investigate if the quick release of diltiazem from the drug products may pose any risks for patients, especially in Brazil where the compounded capsules are prescribed interchangeably with the reference drug.

KEYWORDS: Diltiazem hydrochloride; compounded capsules; dissolution; in vitro dissolution profile.

INTRODUCTION

To obtain registration for generic and similar drugs in Brazil, among other requirements, the manufacturer must submit its products to pharmaceutical equivalence and bioequivalence studies (1, 2).

Pharmaceutical equivalence studies are conducted to prove that two drug products contain the same drug; that is, the salt or ester of the therapeutically active molecule, the dosage form, route of administration, and the concentration or potency are identical. The dissolution test and the comparative study of in vitro dissolution profiles are used to determine the performance of the dosage form (3).

The in vitro dissolution of immediate-release dosage forms is an important tool to ensure batch to batch

quality. Because the dissolution of the dosage form has an important role in drug bioavailability, in vitro dissolution may be utilized to predict the in vivo behavior of a drug product once in vitro–in vivo correlation has been established (4).

Moreover, Brazilian law does not require dissolution testing and a comparative study of in vitro dissolution profiles for compounded drug products. The Brazilian law recommends carrying out dissolution profile studies only for narrow therapeutic index drug products (5).

Diltiazem hydrochloride, chemically 1,5-benzothiazepin-4(5H)-one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride (Figure 1), is a drug widely used in clinical practice. The pharmaceutical dosage forms can be purchased in drug stores (tablets) or compounded in pharmacies (capsules).

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Diltiazem hydrochloride capsules are compounded in the same dosage strengths as those of tablets available on the Brazilian market and are used as a therapeutic alternative to the reference drug product, an approach that is forbidden in the United States (6). Nevertheless, studies comparing the dissolution profiles of compounded capsules and tablets have been reported (7, 8).

The aim of this study was to compare the in vitro dissolution profiles of diltiazem hydrochloride tablets and compounded capsules employing the *USP* dissolution method for tablets.

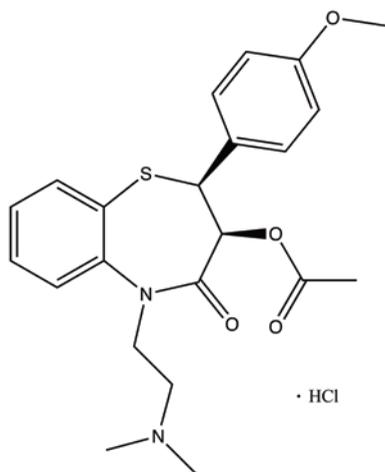


Figure 1. Chemical structure of diltiazem hydrochloride.

MATERIALS AND METHODS

Chemical, Reagents, and Materials

Diltiazem hydrochloride reference standard (100.2% purity) was obtained from the Brazilian Pharmacopoeia (Brasília, DF, Brazil). Ultrapure water for the dissolution tests was obtained from a Gehaka OS10LXE reverse osmosis system (São Paulo, SP, Brazil). Ultrapure water for the chromatographic analysis was obtained from a Millipore system (Bedford, MA, USA). Methanol (HPLC grade) was purchased from J. T. Baker (Phillipsburg, NJ, USA). Trifluoroacetic acid (HPLC grade) was purchased from Tedia (Fairfield, OH, USA).

Instrumentation

HPLC analyses were carried out on a Thermo Finnigan Surveyor System (San Jose, CA, USA) composed of a quaternary pump, degasser, autosampler, column oven, and a photodiode array detector. The chromatographic separation was performed on a Merck Millipore Purospher Star C18 column (150 × 4.6 mm i.d.; 5- μ m particle size), maintained at 30 °C. UV detection was performed at

240 nm. The injection volume was 20 μ L. The mobile phase was a mixture of 0.05% (v/v) trifluoroacetic acid aqueous solution and 0.05% (v/v) trifluoroacetic acid methanolic solution (44:56, v/v) at a flow rate of 1.0 mL/min. The disintegration analyses were carried out on a Nova Ética system (Vargem Grande Paulista, SP, Brazil). The dissolution analysis were carried out on an Agilent Technologies Varian VK7025 dissolution system (Santa Clara, CA, USA). The UV analyses were carried out on a Shimadzu spectrophotometer UV 1800 (Kyoto, Honshu, Japan).

Comparative Analysis of Tablets and Capsule Formulations

The two diltiazem hydrochloride tablets were purchased from a drug distributor at Belo Horizonte, MG, Brazil. Twenty tablets of each formulation were weighed individually, and the weight variation was calculated. The contents of twenty capsules were weighed individually, and the weight variation was calculated employing the method from the *Brazilian Pharmacopoeia* (9). The drug content was determined using the HPLC method previously developed and validated by our group (10). For the tablets, a sample was taken from twenty crushed tablets of each formulation, and for the capsules, a sample was taken from the contents of twenty capsules. The mean peak area and concentration were obtained and used to calculate the percentage of diltiazem in each product. The assays were performed in triplicate. The content uniformity was calculated according to the *Brazilian Pharmacopoeia* (9) and *USP* (11). The disintegration was also verified for all the formulations employing the *Brazilian Pharmacopoeia* and *USP* methods.

Dissolution

The analyses were performed employing the *USP* method (11). The dissolution parameters were water as dissolution medium with Apparatus 2 (paddle) at 75 rpm. Each tablet or capsule was placed in one of the six vessels, each containing 900 mL of purified water. The capsules were first placed inside sinkers to prevent floating. The samples were analyzed at 237 nm, and fresh medium was used as the blank. A calibration curve was used for drug quantification. Samples of 10 mL were withdrawn at 15, 30, 60, 120, 180, and 210 min without medium replacement and immediately filtered with 0.45- μ m PVDF syringe filters. Tablet samples withdrawn at 15 and 30 min did not require dilution. Tablet samples withdrawn at 60, 120, 180, and 210 min and capsule samples required dilution: 4 mL of the dissolution sample was pipetted and diluted to 25 mL with water. At the end of the dissolution test, six samples of each product were also

injected into the chromatograph employing the analytical method previously described to verify drug stability in the dissolution conditions. The presence or absence of degradation peaks in the chromatograms was evaluated.

Preparation of Standard Solutions

Approximately 10 mg of diltiazem hydrochloride was accurately weighed and transferred to a 100-mL volumetric flask, followed by the addition of 50 mL of water. The flask was sonicated for 10 min and filled to the mark with water. Aliquots of the stock standard solution were diluted to obtain standard solutions at the following concentrations: 2.0, 4.0, 6.0, 8.0, 10.0, and 12.0 $\mu\text{g/mL}$. The standard solutions were used to construct a calibration curve and thus to determine drug release in the dissolution tests.

Statistical Analyses

Microsoft Office Excel 2007 was used to calculate the similarity (f_2) and difference (f_1) factors. The similarity factor was calculated only if either the reference or test products released less than 85% of the active ingredient within 15 min with $n = 12$ (12).

RESULTS

The reference drug had an average weight of 186.77 ± 1.80 mg, the generic drug had an average weight of 145.78 ± 1.77 mg, and the compounded capsule had an average content weight of 176.06 ± 4.09 mg. The drug contents of reference, generic, and compounded products were 100.01%, 93.17%, and 98.48%, respectively. All of the products showed suitable acceptance values (AV) for drug content uniformity (3.16, 8.37, and 4.76 for reference drug, generic drug, and compounded capsule, respectively). The reference and generic products did not disintegrate in 30 min, whereas the compounded capsule disintegrated in 5 min.

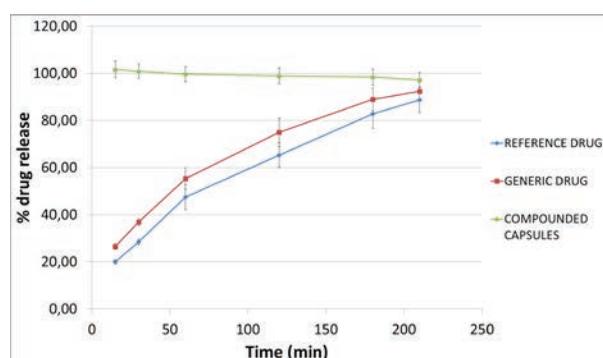


Figure 2. Dissolution profiles of reference and generic drugs and compounded capsules.

The reference and generic products released more than 80% of diltiazem in 3 h, whereas the compounded capsule released more than 80% of diltiazem in only 15 min (Figure 2). The f_2 value of 56.60 and f_1 value of 12.73 were obtained for the generic product when compared with the reference product. It was not possible to calculate f_2 and f_1 values for the compounded product, because the compounded capsule released more than 85% of the active ingredient in 15 min.

DISCUSSION

The results for average weight determination, assay, uniformity of dosage units, and dissolution were acceptable for the reference and generic drugs. The results for compounded capsules, however, were satisfactory only for content average weight, assay, and uniformity of dosage units.

Tablets are usually obtained by the compression of a mixture of active ingredient and excipients that have different functions and may be formulated to provide immediate or modified release depending on the excipients and the manufacturing processes employed. Hard gelatin capsules disintegrate in contact with water, promptly releasing their contents in the stomach. To improve the release and distribution of capsule contents, disintegrants can be added. Capsules may be produced to show modified release using coated pellets containing the drug (13). Because the compounded capsules analyzed were not formulated with the pellet system, they did not exhibit modified release but readily released their contents into the dissolution medium. The reference and generic drug tablets, on the other hand, were formulated with hydrogenated castor oil, an excipient that provides a delayed drug release in concentrations of 5.0–20.0% (14). However, it is important to discuss whether the observed differences between the dissolution profiles of the compounded capsules and those of the reference drug have any clinical impact.

Studies comparing compounded capsules and tablets of propranolol and prednisone have been reported (7, 8). These studies compared the dissolution profiles of the compounded capsules with those of the respective reference drug tablets. The results show significant differences between them for both drugs and are agree with those obtained in this study.

The diltiazem hydrochloride tablets showed in vitro modified release as evidenced by the dissolution profiles. The dissolution test used in this study has two sampling times, one at 30 min and the other at 3 h. The 30-min

sampling time ensures that diltiazem release from the dosage form is not fast, to comply with the acceptance criterion of a release less than 60% of labeled amount (11). The diltiazem hydrochloride tablets available in the market provide a slow in vivo release, with time-to-peak concentration (T_{max}) between 3 and 4 h (15).

A study conducted by Pool and colleagues (16) demonstrated that immediate-release tablets have equivalent effectiveness to modified-release capsules for the treatment of angina pectoris, with no difference in efficacy or incidence of adverse reactions. Furthermore, a study (17) of diltiazem as monotherapy for the treatment of hypertension demonstrated that diltiazem immediate-release tablets have good efficacy when taken three to four times a day.

However, some studies (18–20) have demonstrated the potential risks of calcium antagonists formulated in immediate-release dosage forms for the treatment of hypertension in patients with coronary heart disease. Immediate-release pharmaceutical dosage forms of nifedipine caused ischemic events and an increase in coronary mortality when used at high doses. There are some inconsistent reports regarding adverse reactions related to the immediate-release formulations of nifedipine, diltiazem hydrochloride, and verapamil hydrochloride. Therefore, it is preferable to treat hypertension with long lasting calcium channel blockers or prolonged-release formulations.

Randomized clinical trials (21) conducted to compare the effects of drugs containing diltiazem, diuretics, beta-blockers or diuretics, and beta-blocker associations followed 10,881 patients from October 1992 to October 1999. The results show that diltiazem is as effective as diuretics, beta-blockers, or a combination of both in the prevention of stroke, acute myocardial infarction, and other cardiovascular events. However, the authors reported that diltiazem immediate-release dosage forms were initially administered, and after 1997 they were replaced by an extended-release formulation. The authors did not provide the explanation for this replacement.

The dissolution test for diltiazem hydrochloride tablets published in 1990 in *USP XXII* (22) was different from the test currently described. The dissolution medium was 900 mL of water at 50 rpm and a time of 45 min. The acceptance criterion was not less than 75% (Q) of the labeled amount of diltiazem hydrochloride tablet released in 45 min. According to the parameters set for the dissolution test, it can be inferred that the diltiazem hydrochloride tablets available at the time were of immediate release.

However, the dissolution test for diltiazem hydrochloride tablets published in 1995 in *USP 23* (23) showed a change, becoming similar to the test currently employed. It used 900 mL of water as the dissolution medium, paddles at 100 rpm, and two sampling times, 30 min and 3 h. The acceptance criterion was no more than 60% of the labeled amount dissolved in 30 min and at least 80% of the labeled amount dissolved in 3 h. Although it is unclear, it can be assumed that the dissolution test was modified because the formulation was altered to target a modified drug release, possibly due to the reports of increased risk of cardiovascular events in patients using immediate-release tablets of calcium antagonists.

CONCLUSION

Results for generic and reference drugs were acceptable for all tests. Furthermore, the generic and reference drug dissolution profiles were similar. Test results for the compounded capsules were not acceptable only for the dissolution test. The dissolution profile of the compounded capsule was different from that of the reference drug, wherein the capsules readily released the active ingredient while tablets presented a prolonged-release mechanism. Therefore, it is necessary to investigate if the use of diltiazem immediate-release dosage forms may cause adverse cardiovascular effects. Moreover, prescribers should be aware of the pharmacokinetic differences and possible risks related to the use of diltiazem compounded capsules, especially in Brazil, where the compounded capsules are prescribed interchangeably with the reference drug.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding this manuscript.

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