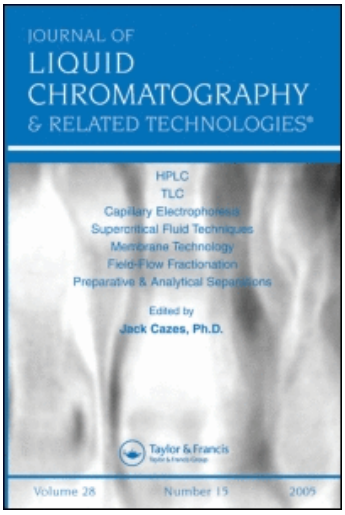

Journal of Liquid Chromatography & Related Technologies

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

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Online publication date: 26 March 2003

To cite this Article Aboul-Enein, Hassan Y. , Hussein, Rajaa F. , Radwan, Mahasen A. , Yusuf, Ahmad , Al-Ahmadi, Wijdan and Al-Rawithi, Sameer(2003) 'Tamsulosin Dissolution from Pharmaceutical Dosage Forms Using an Automated HPLC System', Journal of Liquid Chromatography & Related Technologies, 26: 7, 1109 — 1116

To link to this Article: DOI: 10.1081/JLC-120020097

URL: http://dx.doi.org/10.1081/JLC-120020097


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JOURNAL OF LIQUID CHROMATOGRAPHY & RELATED TECHNOLOGIES®
Vol. 26, No. 7, pp. 1109–1116, 2003

Tamsulosin Dissolution from Pharmaceutical Dosage Forms Using an Automated HPLC System

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ABSTRACT

A novel, rapid, accurate, and sensitive high-performance liquid chromatographic assay was developed to determine tamsulosin (TAM) in pharmaceutical dosage forms and to follow its dissolution pattern. An efficient separation of TAM was performed using stainless steel Supelcosil LC-18

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DOI: 10.1081/JLC-120020097 1082-6076 (Print); 1520-572X (Online)

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column (25 cm × 4.6 mm; 5 μm particle size) preceded by a Sentry guard column. The mobile phase consisted of an aqueous solution containing acetonitrile 70% (pH 3.4 adjusted with glacial acetic acid) and delivered at a flow rate of 0.75 mL/min. The compound of interest was detected using photodiode array detector at 225 nm. Under these conditions, the retention time for TAM was 6.1 ± 0.2 min. The detector response was linear for TAM in alkaline solution ($r > 0.9975$) in the range of 0.025–1.00 μg/mL. The detection and the quantification limits for TAM were 0.015 and 0.025 μg/mL, respectively. No interferences were observed from the capsule's excipients. The drug content in each capsule ranged from 99 to 101%. The dissolution study of OMNIC® capsules revealed that TAM in USP media (pH 1.2) showed no dissolution up to 12 h. However, a first order release kinetic, with dissolution $T_{50\%}$ of about 2 h, was observed in USP media (pH 7.4).

Key Words: Tamsulosin; Photodiode array detector; Dissolution; HPLC.

INTRODUCTION

Tamsulosin hydrochloride (TAM), (-)-(R)-5-[2-[[2-(o-ethoxyphenoxy)-ethyl]amino]propyl]-2-methoxybenzenesulfonamide hydrochloride (Fig. 1), is a structurally new type of sulfonamide derivative, possessing a highly selective α_1-adrenoceptor antagonistic property. An in vitro study revealed that the selectivity of this drug to prostate α_1-adrenoceptor was about 10 times higher than that to aorta α_1-adrenoceptor.[1,2] Peak serum levels are achieved 4–8 h after oral administration of controlled release TAM; bioavailability approaches 100%; it is approximately 99% protein bound, and it has an elimination half-life of 9–15 h.[3] Tamsulosin has produced modest symptomatic and urodynamic improvement in patients with benign prostatic hyperplasia. Very few methods for the assay of TAM have been published.[4–7] However, these methods are not suitable for the assay of TAM in pharmaceutical dosage forms, as some of these methods are more sophisticated and the equipment needed is not normally found in the common clinical laboratory. To the best of our knowledge, no method has been reported in the literature for the determination of TAM in the pharmaceutical capsule dosage form. When a poor water-soluble drug is orally administered, its dissolution could be the rate-limiting step for its in vivo absorption and, hence, its onset of action. Therefore, drug dissolution testing is an integral part of pharmaceutical development and routine quality control monitoring of drug release characteristics. The aim of this investigation is to develop a new, rapid, sensitive, simple, and direct high-performance liquid chromatographic (HPLC) procedure with a photodiode array detector, for the quantitation of TAM in pharmaceutical formulation, and to evaluate its in vitro dissolution rate.

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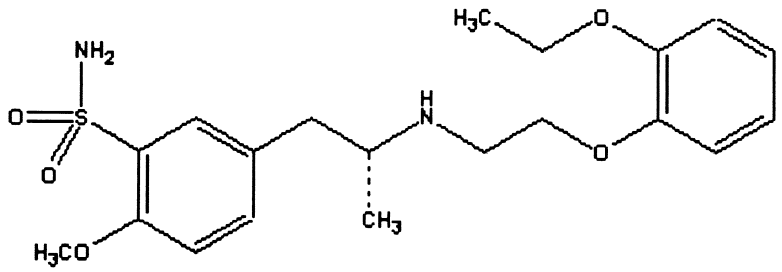

Figure 1. Structure of TAM.

EXPERIMENTAL

Chemicals and Reagents

The HPLC grade acetonitrile, phosphoric acid 85%, and hydrochloric acid were purchased from Fisher Scientific Co. (Fairlawn, NJ). Disodium hydrogen phosphate (Na_2HPO_4) was supplied from Fluka (Buchs, Switzerland). Glacial acetic acid was obtained from BDH Chemicals (Poole England). High-performance liquid chromatographic grade water was prepared by reverse osmosis and further purified by passing through a Milli-Q System (Millipore Company, Milford, MA). Pure TAM was kindly provided by Boehringer Ingelheim (Germany). OMNIC® capsules containing tamsulosin hydrochloride (0.4 mg per capsule) were obtained from the local market and manufactured by SAJA pharmaceuticals, Jeddah, Saudi Arabia. A stock solution of TAM (1 μg/mL) was prepared in 0.02 N Na_2HPO_4 pH 7.4 adjusted with phosphoric acid. This stock solution was prepared weekly and further diluted to produce concentrations of tamsulosin that ranged from 0.025 to 1.00 μg/mL (0.025, 0.05, 0.1, 0.2, 0.4, 0.6, 0.8, and 1.00 μg/mL). The stock solutions were stored in the dark at −70°C until needed during the week. No instabilities were observed from solutions stored under these conditions compared to fresh daily-diluted ones, since there was no observed change in TAMs peak height or no appearance of any impurities.

Instrument and Chromatographic Conditions

A HPLC system, Waters Alliance, dissolution system (Waters Associates, Inc. Milford, MA) consists of Waters 2690D Separation Module with an eight-needle dissolution dispenser, Waters Transfer Module, with eight syringes, one dissolution test bath (Hanson Research SR8-Plus), eight Uni-Probes, one for

each dissolution vessel to be sampled, and Waters 996 Photodiode array detector. The compound of interest was detected at 225 nm. The data were collected with a Millennium^{32} Chromatography Manager data collection system utilizing a Pentium 4 computer connected to Inkjet HP PSC 750 printer. Tamsulosin determination was performed using a stainless steel Supelcosil LC-18 column (25 cm × 4.6 mm; 5 μm particle size) preceded by a Sentry guard columns. The mobile phase consisted of an aqueous solution containing acetonitrile (70%), adjusted to pH 3.4 with glacial acetic acid, and delivered at a flow rate of 0.75 mL/min.

In Vitro Dissolution Studies

The dissolution rates of TAM from capsules were performed on Hanson SR8-Plus dissolution apparatus (USA). Drug release tests were carried out according to conventional USP XXIII dissolution procedures for the single-entity products, with the use of a paddle-stirrer type of apparatus in 500 mL of 0.02 N Na_2HPO_4 (pH 7.4 using phosphoric acid, to simulate intestinal medium), at a stirring rate of 100 rpm for 10.5 hrs, then at infinity (250 rpm) for the rest of the dissolution period. The temperature of the cell was maintained at $37 \pm 0.5^{\circ}C$ by using a thermostatic bath. At each sample time interval, an exact volume of sample was withdrawn from each flask and immediately replaced with an identical volume of fresh medium to maintain a dissolution sink condition. A correction factor was included in the calculations to account for the drug lost in the samples. At predetermined time intervals (0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 10.5, and 11 hrs), the concentrations of TAM (μg/mL) in the dissolution medium were determined by the proposed HPLC.

Analysis of Pharmaceutical Dosage Form

Preparation of Tamsulosin Standard Solution

A stock solution of pure TAM (1 μg/mL) was prepared in methanol. This stock solution was further diluted with 0.02 N Na_2HPO_4, pH 7.4, adjusted with phosphoric acid to produce concentrations of TAM that ranged from 0.025 to 1.00 μg/mL (0.025, 0.05, 0.1, 0.2, 0.4, 0.6, 0.8, and 1.00 μg/mL).

Preparation of Tamsulosin Solution from Capsules

Three different stock solutions of OMNIC capsules containing (0.4 mg) tamsulosin hydrochloride was prepared in 500 mL 0.02 N Na_2HPO_4, pH 7.4, adjusted with phosphoric acid to produce concentration of (0.8 μg/mL).

For the concentration of 0.8 μg/mL, we found an average amount per capsule (drug content) ± SD was 0.396 mg ± 0.001, while the average recovery percentage ± SD of TAM capsules, in comparison to the pure TAM, was 99% ± 0.25 ($n = 3$).

Data Analysis

All data were reported as the mean ± SD of at least eight parallel studies. The results were calculated by linear regression without weighing, using the formula: $Y = a + bX$, where Y is the peak height of the drug; a is the intercept; b is the slope; and X is the concentration of TAM. The amount of TAM, obtained from the drug dissolution studies, was calculated from the calculated linear regression equation. The in vitro dissolution data ($n = 8$) were analyzed to fit a kinetic order for release. The student's t-test was used to determine statistically significant differences ($p < 0.05$) for in vitro data.

RESULTS AND DISCUSSION

A specific and reproducible HPLC method was developed in our laboratory for TAM. The method was rapid and convenient, and under the conditions described, TAMs retention time was 6.1 ± 0.2 min. The correlation coefficient (r) was >0.9975 ± 0.0015 for the tested concentration range from 0.025 to 1.00 μg/mL ($n = 8$). The detection limit under these conditions, defined as three times the level of noise for TAM in blank samples, was 0.015 μg/mL, while the quantification limit of this method was 0.025 μg/mL. To demonstrate the utility of the method, Fig. 2 depicts three representative chromatograms including a blank sample (A); a sample supplemented (B) with 0.4 μg/mL of TAM, and the third sample (C), calculated concentration of 0.8 μg/mL and collected 10 hr after starting the capsule dissolution.

Table 1 shows the mean TAM content in the capsule dosage form. For the tested capsules, $n = 8$ (0.4 gm/capsule), the mean drug content was 0.396 ± 0.001 mg.

The dissolution study of OMNIC capsules revealed that tamsulosin in USP media (pH 1.2) showed no dissolution up to 12 h. However, a first order release kinetic, with dissolution $T_{50\%}$ of about 2 h, was observed in USP media (pH 7.4). Tamsulosin showed no release pattern in USP gastric media (pH 1.2) up to 12 h, which could explain the reported delay of its peak serum level in humans from 4 to 8 h[3] after the capsule's administration. The in vitro dissolution profile of TAM capsule in USP intestinal media (pH 7.4) is shown in Fig. 3. For each plotted point, the mean reading of eight capsules

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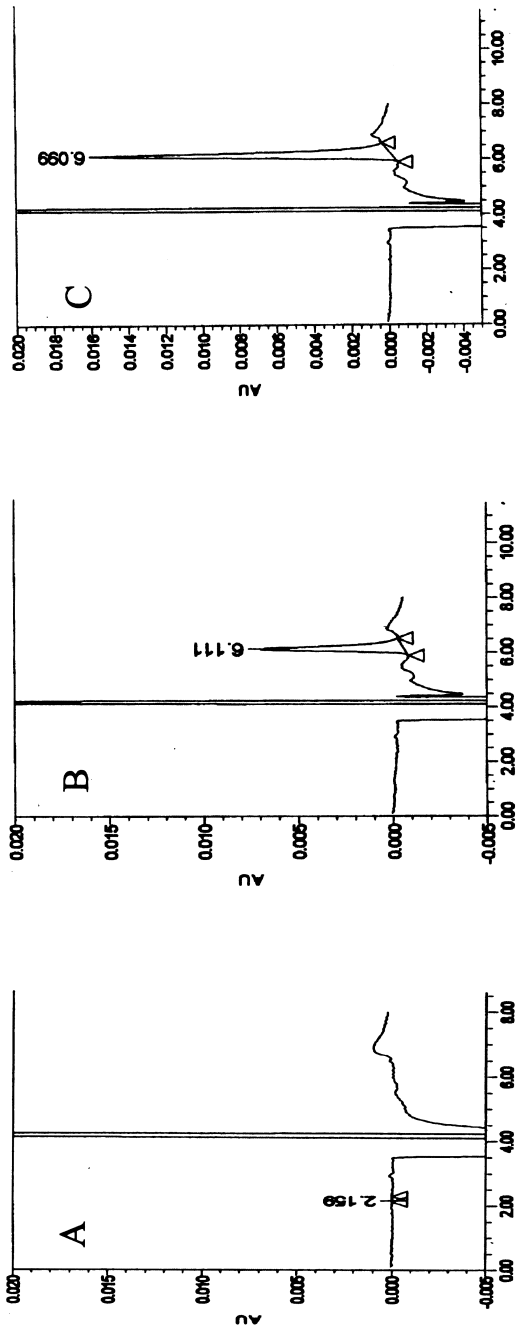

Figure 2. Chromatograms of a blank sample (A); a sample supplemented (B) with 0.4 μg/mL of pure TAM powder; and the third sample (C), calculated concentration of 0.8 μg/mL, collected 10 hr after starting the capsule dissolution.

Table 1. The mean (±SD) TAM content in capsule dosage form.

Label claim (mg/capsule[a])	0.4
Measured amount (mg/capsule)	0.396 (±0.001)
Percentage of total amount per capsule dosage form	99 (±0.25)

[a]Average of eight determinations.

is shown expressed as percent TAM released. The dissolution data of TAM, at this pH, showed a little higher RSD% (6.8–12.3%) at lower drug concentrations (<0.4 μg/mL). On the other hand the RSD% was 1.4–9.3% for TAM concentrations >0.4 μg/mL. Therefore, the utilized automated dissolution-HPLC system produced precise and reproducible results. Tamsulosin dissolution in simulated intestinal media was biphasic following a first order release kinetics with dissolution $T_{50\%}$ of 1.98 h. Almost all the drug was released (at pH 7.4) from the capsule within 12 h.

In conclusion, the fully automated dissolution-HPLC system used was rapid, reproducible, and convenient for TAM detection in pharmaceutical dosage forms and required no internal standard.

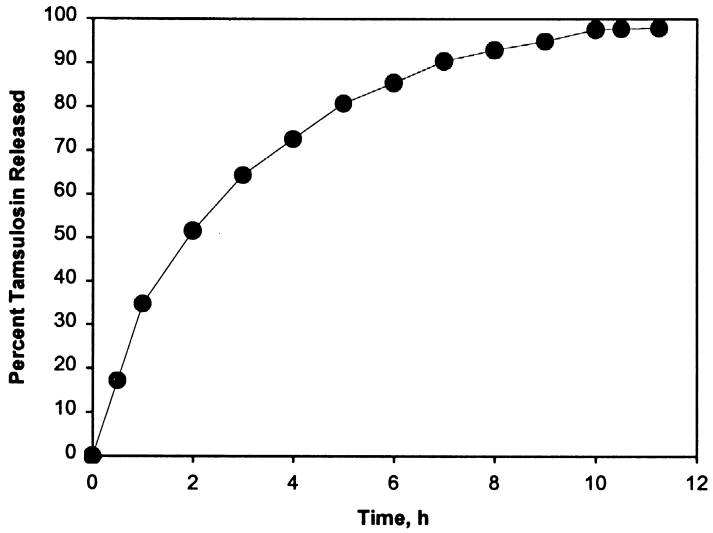

Figure 3. The in vitro mean dissolution profile of TAM capsules in USP intestinal media (pH 7.4). Average of eight determinations.

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Received November 10, 2002
Accepted December 14, 2002
Manuscript 6013