



Research paper

Pharmaceutical evaluation of atorvastatin calcium tablets available on the Internet: A preliminary investigation of substandard medicines in Japan



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ABSTRACT

Substandard medicine is a type of substandard/spurious/falsely labeled/falsified/counterfeit (SSFFC) drug as defined by the WHO that has permeated the distribution of drugs on the Internet, and is accessible without prescription. An influx of substandard medicines is thus a serious matter in many developed countries. Here, Lipitor and its generic drugs containing atorvastatin calcium (ATC), used for the treatment of hyperlipidemia worldwide, were selected as a model prescription drug. Six brands of ATC tablets were purchased from four Japanese-language web sites. Raman spectroscopy and powder X-ray diffraction (PXRD) were employed to determine ATC and ingredients in the tablets. Although PXRD measurements showed no diffraction peaks of ATC because of its low content, a handheld Raman spectrometer detected ATC in unmodified tablets (without crushing). The tablets were assayed for drug content and dissolution profile according to the Japanese Pharmacopoeia, and one product showed an obviously slower drug release. X-ray computed tomography (CT) showed the interior of the tablet in detail and suggested that massive agglomerations caused slow disintegration of the tablet. This is the first report applying X-ray CT to tablets obtained on the Internet and indicates that unqualified prescription drugs are easily distributed on the Internet without any quality assurance.

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1. Introduction

Substandard medicine is a type of substandard/spurious/falsely labeled/falsified/counterfeit (SSFFC) drug, defined as a generic term for diversely problematic medicines by the World Health Organization [1,2]. SSFFC drugs distributed globally have sometimes caused fatal damage and antimalarial drugs in particular are a typical example in developing countries [3,4]. SSFFC drugs have now permeated Internet drug sales, and are accessible without prescription by nonspecialists in developed countries, even though the distribution route of prescription drugs is well organized. Drugs

imported from foreign countries via Internet sales may be approved in the country of origin; however, the drugs are not always approved in the country to which they are exported. Therefore, an influx of substandard medicines is a serious matter in many developed countries [5–8].

For the medicines to treat lifestyle diseases such as erectile dysfunction or obesity, it is estimated that Internet sales are the preferred purchasing route to avoid face-to-face communication. In that case, any problems are unlikely to be disclosed publicly until serious health hazards occur on a large scale. However, there have been fatal accidents, and people recognized this problem because the mass media reported the event sensationally. These facts suggest that nonspecialists can easily access prescription drugs, which are otherwise strictly regulated and distributed domestically. In the treatment of a chronic disease, once medication is begun, it would often continue for life. If the same content is repeated in the

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prescriptions, it is called a “ditto” or “do” prescription. Nowadays, some patients consider purchasing their drugs on the Internet at a lower price. Indeed, there are numerous Web sites selling drugs on the Internet, and products having almost the same appearance and packaging as the original brand are imported across borders [9].

Medicines distributed overseas may be imported into Japan for personal use for noncommercial purposes and in line with the products regulated by the Ministry of Health, Labour and Welfare [10]. Kimura et al. noted that most such imported medicines were purchased from Internet traders and several examples of counterfeit prescription drugs have been reported [9,11]. Despite the current situation, to our knowledge, few studies have evaluated the pharmaceutical quality of drugs purchased on the Internet in detail.

In this study, Top 3 web sites which appear in the internet search were selected in this research. We focused on Lipitor, which was superseded to numerous generic drugs containing atorvastatin calcium (ATC) with patent expired. Lipitor tablets 10 mg—used worldwide for the treatment of hyperlipidemia—were selected as a model prescription drug. Recently numerous generic drugs containing atorvastatin calcium (ATC) have been developed and commercialized. Several different brands of tablets were purchased online from web sites, and we tested the contents and dissolution behavior of the active pharmaceutical ingredient (API). In addition, a simple identification method was studied by using a handheld Raman spectrometer. In previous work, chemical imaging of drugs purchased from Internet traders has been reported by using near-infrared (NIR) [12,13] and Raman microspectroscopy [14]. In the present study, X-ray computed tomography (CT) was employed to observe the interior of tablets purchased on the Internet in detail.

2. Materials and methods

Atorvastatin calcium trihydrate was purchased from Tokyo Chemical Industry Co. (Tokyo, Japan) and used as the standard reagent. Lipitor tablet 10 mg (Astellas Pharma Inc, Tokyo, Japan) was

used as the standard tablet. All other chemicals were reagent grade. Japanese-language Internet web sites selling drugs, which were continuously accessible during the study period, were searched. Six brands of tablets (10 mg) that were available online were found using the keyword “lipitor”, and a code number (J1–J6) was assigned for each tablet (Table 1). All experiments were performed in triplicate.

2.1. Pharmacopoeial evaluation of ATC tablets

Determination of API content and the dissolution test were performed according to the Japanese Pharmacopoeia 16th edition (JP16). The experimental procedure was as follows.

2.1.1. Determination of API content



















One tablet was disintegrated by shaking with 60 mL of 50% methanol solution; 10 mL of the internal standard solution (0.4 mg/mL 1,3-dinitrobenzene methanol solution) was added and diluted in a measuring cylinder to 100 mL total. This was then centrifuged and supernatant was used as the test solution for high performance liquid chromatography (HPLC) measurements.

HPLC conditions included the following: mobile phase, water/ acetonitrile/THF (11:8:6); column, Inertsil ODS-3 (4.6 mm i.d. × 250 mm, GL Sciences, Tokyo, Japan); column temperature, 30 °C; wavelength, 244 nm; flow rate, 1.0 mL/min; injection volume, 10 µL.

2.1.2. Dissolution test (JP16, apparatus 2)

One tablet was used for a dissolution test with apparatus 2 according to JP16. The test solution was sampled after 5, 10, 15, 20, and 30 min and filtered through a membrane filter (0.45 µm). Test solution: 900 mL of distilled water; rotation speed, 75 rpm; temperature, 37 °C.

Table 1
Atorvastatin calcium tablets (10 mg) purchased on the Internet.

Web site	Code	Trade name	Package (on web site)	Package (sent item)	Appearance of sheet	Country	Package leaflet	Received date	Expiration date	Price/tab (Yen)
KAIGAI-DRUG	J1	Aztor (generic Lipitor)				India	×	2012/1/31	2014/7/1	106.7
BAYON MEDICAL SERVICE	J2	Lipitor				Thailand	○	2011/12/15	2014/1/1	139.3
	J3	Lipiget (generic Lipitor)				Pakistan	○	2011/12/15	2014/5/1	115.0
kusuriya3.com	J4	Atorlip (generic Lipitor)				India	×	2011/12/20	2013/11/1	44.7
	J5	Lipvas (generic Lipitor)				?	×	2011/12/20	2012/6/1	53.0
Best KUSURI	J6	Lipitor				Germany	○	2011/12/15	2013/10/1	159.3

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