Saudi Pharmaceutical Journal (2015) **23**, 504–514

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Why sildenafil and sildenafil citrate monohydrate crystals are not stable?

Somchai Sawatdee [a,b], Chaveng Pakawatchai [c], Kwanjai Nitichai [d], Teerapol Srichana [a,e,*], Hirihattaya Phetmung [d,*]

[a] *Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand*
[b] *Drug and Cosmetic Research and Development Group, School of Pharmacy, Walailak University, Thasala, Nakhonsithammarat 80161, Thailand*
[c] *Faculty of Sciences, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand*
[d] *Inorganic and Materials Chemistry Research Unit, Department of Chemistry, Faculty of Science, Thaksin University, Songkhla 90000, Thailand*
[e] *Nanotec-PSU Excellence Center on Drug Delivery System, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand*

Received 17 November 2014; accepted 19 January 2015
Available online 24 January 2015

KEYWORDS

Sildenafil;
Sildenafil citrate monohydrate;
Solution crystallization;
Antisolvent addition;
Slow solvent evaporation;
Stability

Abstract Sildenafil citrate was crystallized by various techniques aiming to determine the behavior and factors affecting the crystal growth. There are only 2 types of sildenafil obtaining from crystallization: sildenafil **(1)** and sildenafil citrate monohydrate **(2)**. The used techniques were (i) crystallization from saturated solutions, (ii) addition of an antisolvent, (iii) reflux and (iv) slow solvent evaporation method. By pursuing these various methods, our work pointed that the best formation of crystal **(1)** was obtained from technique no. (i). Surprisingly, the obtained crystals **(1)** were perfected if the process was an acidic pH at a cold temperature then perfect crystals occurred within a day. Crystals of compound **(2)** grew easily using technique no. (ii) which are various polar solvents over a wide range of pH and temperature preparation processes. The infrared spectroscopy and

* Corresponding authors at: Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand. Tel.: +66 (0)74288842; fax: +66 (0)74248148 (T. Srichana), Inorganic and Materials Chemistry Research Unit, Department of Chemistry, Faculty of Science, Thaksin University, Songkhla, 90000, Thailand. Tel.: +66 (0)919815633; fax: +66 (0)74443946 (H. Phetmung).
E-mail addresses: teerapol.s@psu.ac.th (T. Srichana), tayaphetmung@yahoo.com (H. Phetmung).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2015.01.019

nuclear magnetic resonance spectra fit well with these two X-ray crystal structures. The crystal structures of sildenafil free base and salt forms were different from their different growing conditions leading to stability difference.

1. Introduction

The crystal structures of drug compounds or proteins acting as receptors in human physiological processes have been of interest in order to obtain a better understanding of molecular structure and drug-receptor interactions (Zhang et al., 2012; Datta and Grant, 2004). Generally, the searching and improving methodology for those compounds are continuously under investigation. Traditionally, the crystal structure of drugs can be determined from a single crystal X-ray diffraction technique, which is the most straightforward tool for elucidating crystal and molecular structures. However, it is difficult and time consuming to prepare single crystals of drugs and the crystals are easily dehydrated (Guo et al., 2011).

The discovery of sildenafil began by the efforts of Nobel Prize winners Furchgott, Ignarro and Murad who also had discovered the link between nitric oxide (NO) and the human cardiovascular system. These research workers took this finding and developed a new ring system hoping to produce new drugs that would potentiate the effects of NO on the cardiovascular system such as UK-92-480, later known as sildenafil. This molecule was synthesized for the purpose of modifying NO production not only for a clinical study but also for its launch in the market after the US FDA approved it on 27 March 1998 (McCullough, 2002). Sildenafil and its derivatives or salts are highly potent pharmaceutical drugs that selectively inhibitor of cyclic guanosine monophosphate (cGMP) and are specific as a phosphodiesterase-5 (PDE-5) inhibitor. By inhibiting the hydrolytic breakdown of cGMP, sildenafil prolongs the action of cGMP. This results in augmented smooth-muscle relaxation (Raja et al., 2006; Nichols et al., 2002). Sildenafil was also the first oral agent used for the medical treatment of erectile dysfunction and has been subsequently shown to have important effects on the pulmonary vasculature and because of that has been recently used for the treatment of pulmonary hypertension (PH) (Chockalingam et al., 2005; Nichols et al., 2002; Galiè et al., 2009). Due to low water solubility of sildenafil, the manufacturer improved its water solubility by salt formation as sildenafil citrate.

The molecular structures of sildenafil ($C_{22}H_{30}N_6O_4S$) (**1**) known chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo [4, 3-*d*] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine. Sildenafil citrate and sildenafil citrate monohydrate ($C_{28}H_{40}N_6O_{12}S$) (**2**) are shown in Fig 1 (Al-Omari et al., 2006).

From the literature, there have been previous reports on the crystallization techniques used for sildenafil (Stepanovs and Mishnev, 2012), its citrate salt (Yathirajan et al., 2005) and saccharinate salt (Banergee et al., 2006). The basic sildenafil crystal was prepared from sildenafil citrate by reaction with a stoichiometric amount of aqueous KOH solution. The citrate salt was then separated from the sildenafil molecule. The crystal is a monoclinic system, with the space group $P2_1/c$ and unit cell parameters of a = 17.273(1), b = 17.0710(8), c = 8.3171 (4) Å, β = 99.326(2)°, Z = 4, V = 2420.0(3) Å^3 (Stepanovs and Mishnev, 2012). Sildenafil citrate monohydrate was prepared by recrystallization from dimethylformamide. The crystal was orthorhombic with the space group *Pbca* and unit cell parameters of a = 24.002(4), b = 10.9833(17), c = 24.363(3) Å, Z = 8, V = 6422.9(17) Å^3 (Yathirajan et al., 2005). In addition, sildenafil saccharinate was prepared by grinding 1:1 M proportions of dry sildenafil and saccharin. The crystal of sildenafil saccharinate was triclinic, with space group $P1$ and unit cell parameters of a = 10.3848(10), b = 11.1915(11), c = 14.3155(14) Å, Z = 2, V = 1546.5(3) Å^3 (Banergee et al., 2006). Sildenafil had a pK_{a1} value of 9.84 at its amide (pyrimidine ring) and a pK_{a2} value of 7.10 at its tertiary amine (piperazine ring) (Al-Omari et al., 2006). The solubility of sildenafil depends on pH of solvent and its pK_a which affects the crystal growth of sildenafil. In addition, the co-crystals of sildenafil with co-former agent were reported (Sanphui et al., 2013; Zegarac et al., 2007). The crystals of sildenafil and sildenafil citrate monohydrate reported in the literatures (Stepanovs and Mishnev, 2012; Yathirajan et al., 2005) were unstable as the R value was still high. Hence this study aimed to prepare sildenafil crystal and analyze crystallization data together with molecular interaction.

We hope to understand the crystal growth behavior and optimize the quality of single crystals. Growth from solution

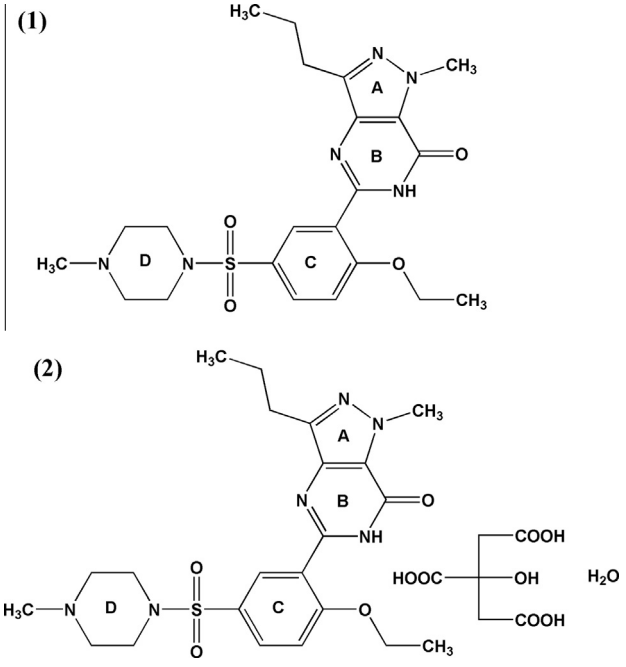

Figure 1 Chemical structures of sildenafil **(1)** and sildenafil citrate monohydrate **(2)**.