ISSN: 0975-766X
CODEN: IJPTFI

Available Online through ***Research Article***

www.ijptonline.com

IMPROVEMENT OF THE WATER-SOLUBILITY OF PACLITAXEL WITH AN AMORPHOUS SOLID DISPERSING TECHNIQUE USING POLYVINYLPYRROLIDONE AS HYDROPHILIC CARRIER

Masaaki Katsuki[1*], Mitsuru Irikura[1], Hiroshi Moriuchi[2], Masao Ohmitsu[2], Toshio Kubota[2], Daisuke Iohara[3], Fumitoshi Hirayama[3], Toru Otori[4], Kenji Matsuyama[5]

[1]Department of Clinical Pharmacy, Daiichi University of Pharmacy, Japan.

[2]Center of Pharmaceutical Care for Community Health, Daiichi University of Pharmacy, Japan.

[3]Faculty of Pharmaceutical Sciences, Sojo University, Japan.

[4]Faculty of Pharmacy, Kindai University, Japan.

[5]Center for Supporting Pharmaceutical Education, Daiichi University of Pharmacy, Japan.

Email: m-katsuki@daiichi-cps.ac.jp

Received on: 08-04-2019 *Accepted on: 30-06-2019*

Abstract

Objective: The present study aimed to improve the solubility of the poorly water-soluble paclitaxel (PTX) using an amorphous solid dispersing technique with polyvinylpyrrolidone (PVP) as a hydrophilic carrier and to develop a new formulation of PTX without cremophor EL (ethanol polyethoxylated castor oil = 1:1) as a solvent.

Methods: We attempted to stabilize PTX in an amorphous form by preparing an amorphous solid dispersion with PVP. Then, we evaluated the potential of the amorphous PTX–PVP solid dispersion using powder X-ray diffraction and dissolution testing.

Results: The sharp peak of PTX was observed in the 2θ value of 12°–13° range using the powder X-ray

diffractometer (PXRD). This sharp peak changed into a broad peak in the amorphous PTX–PVP solid dispersion. Dissolution testing revealed that the amorphous PTX–PVP solid dispersion had improved aqueous solubility compared with native PTX.

Conclusion: These results showed that amorphization of PTX using PVP was achieved and that we have developed a new formulation of PTX without using cremophor EL as the solvent.

Keywords: Paclitaxel, Polyvinylpyrrolidone, Amorphous solid dispersion, Cremophor EL-free.

1. Introduction

Paclitaxel (PTX) is a diterpenoid pseudoalkaloid, comprising a taxane ring and an N-benzoyl-phenyl-isoserine group, with the molecular formula $C_{47}H_{51}NO_{14}$ (Fig. 1) and a corresponding molecular weight of 853 Da. It is a precursor drug of the class of taxanes, working as a stabilizing agent for microtubules [1].

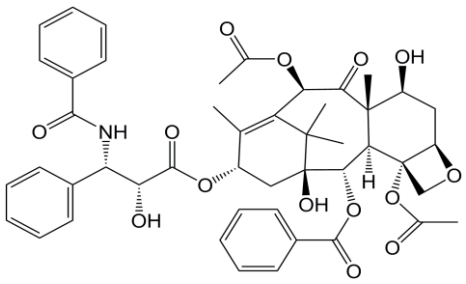

Figure 1: Chemical structure of paclitaxel.

PTX is isolated from the bark of *Taxus brevifolia* and is largely used as an antitumor drug [2]. The formulation of PTX known as Taxol® employs a mixture of cremophor EL and dehydrated ethanol because of its low solubility in water. However, Taxol® causes unwanted side effects, including nephrotoxicity, neurotoxicity, and hypersensitivity reactions, due to the presence of cremophor EL® and ethanol in the formulation [3].[4]. Therefore, clinical use of PTX requires preventive prior glucocorticoid and antihistamines

administration together with a 3-hour slow infusion of PTX, resulting in great inconvenience to patients[5].

Nanoparticle albumin-bound PTX (nab-PTX) is a cremophor EL-free, 130-nanometer particle form of PTX that has been approved by the Food and Drug Administration, in January 2005, as a treatment for breast cancer [6]. Compared with conventional solvent-based PTX (sb-PTX), this new formulation circumvents cremophor EL®-related toxicities and allows for a shorter infusion period as well as eliminates the need for steroid and antihistamine premedication. In addition, a recent pharmacokinetic/pharmacodynamic study demonstrated that nab-PTX, in preclinical xenograft models, achieved a higher concentration of PTX delivery and a higher mean free PTX maximum serum concentration compared with sb-PTX [7]. However, because nab-PTX contains an albumin derived from human blood as an additive, the risk of related infection cannot be completely excluded [8].

There are numerous aqueous solubility- and dissolution rate-enhancing techniques, including particle size reduction or surface area enhancement, nanoparticles, salt forms, surfactant use, cyclodextrin complex developments, amorphous solid dispersions (hydrophilic polymeric drug delivery systems), and encapsulations [9]. These techniques have been effectively used in improving the aqueous solubility and dissolution rate of several natural and synthetic compounds [10]-[12]. The amorphous solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs, such as ketoprofen [13], tenoxicam [14], nifedipine [15], nimodipine [16], ursodeoxycholic acid [17], and albendazole [18]. PVP (polyvinylpyrrolidone) has been used for the preparation of amorphous solid dispersions as a component of the binary system for various drugs, such as sulindac [19], fenofibrate [20], tacrolimus [21], and flurinazine [22]. Therefore, amorphous solid dispersion represents a promising formulation strategy.

The present work aimed to evaluate the potential of the amorphous solid dispersion technique for developing a formulation of PTX using PVP (Fig. 2) as the hydrophilic carrier that would be cremophor EL solvent-free.

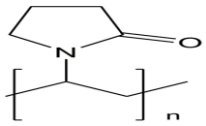

Figure 2: Chemical structure of polyvinyl pyrrolidone.

2. Experimental

Materials

PTX was purchased from Tokyo Chemical Industry Co., Ltd. PVP and ethanol was purchased from Sigma. Otsuka normal saline was purchased from Otsuka Pharmaceutical Co., Ltd. All chemicals were of analytical reagent grade, and solutions were prepared with Millipore purified water.

Methods

Preparation of PTX–PVP amorphous solid dispersion

A mixture of PVP and PTX (1:4 by weight) was added to 2 mL ethanol and kneaded thoroughly for about 10 mints to form a clear paste in an agate mortar (Fig.3). Then, the paste was dried under vacuum for 24 hours.

Figure 3: Photograph of PTX and PVP in ethanol after they were kneaded thoroughly for about 10 minutes.

Powder X-ray diffractometer

Each powder was subjected to a powder x-ray diffractometer (PXRD) and scanning electron microscopy (SEM) to confirm the complexation. PXRD was performed by means of a Rigaku-RINT Ultima + diffractometer (Tokyo, Japan) under the following conditions: Ni-filtered Cu-Kα radiation (1.542 Å), 40 kV, 40 mA, divergent slit of 1.74 mm (1°), scanning slit of 0.94 mm (1°), receiving slit of 0.15 mm, and goniometer angular increment of 5°/min. SEM observations were carried out with a Hitachi TM-3000 (Tokyo, Japan).

Dissolution testing

Each powder was added to 0.5 mL ethanol. The first powder contained only PTX (4 mg). The second powder was a mixture of PTX (4 mg) and PVP (16 mg). The third powder was the PTX–PVP (20 mg) amorphous solid dispersion. Subsequently, each solution was added to 50 mL Otsuka normal saline by stirring. The solubility was visually assessed by examining whether the powder crystal was completely dissolved or seemed insoluble.

3. Results and discussion

PXRD Analysis

Each powder was subjected to PXRD and SEM to confirm the complexation. As shown in Fig. 4–7, each powder shows unique diffraction peaks that can be used for identification. PTX had strong characteristic diffraction peaks at a 2θ value of 12°–13° (Fig. 4). PVP had broad peaks at 2θ values of 11°–14° and 18°–24° (Fig. 5). The mixture of PTX and PVP had sharp peaks at a 2θ value of 12°–13° and broad peaks at a 2θ value of 18°–24° (Fig. 6). On the other hand, PTX amorphization using PVP had characteristic

diffraction peaks (Fig. 7). The strong, sharp peak derived from PTX in the amorphous PTX using PVP had changed into the broad peaks at a 2θ value of 10°–14°. However, the broad peak derived from PVP had not changed at 18°–24° value of 2θ. Amorphous forms do not have crystal characteristics, i.e., atoms do not form a regular line. Therefore, it becomes the amorphous evidence that a peak does not appear in PXRD. However, an amorphous form can often present with partial crystal characteristics. In addition, the crystal can be more disordered when the atom distance is complete is thought. Thus, the amorphous form displays a peak that is not sharp and appears broad. Taken together, these results suggested that the amorphous solid dispersion of PTX and PVP was achieved.

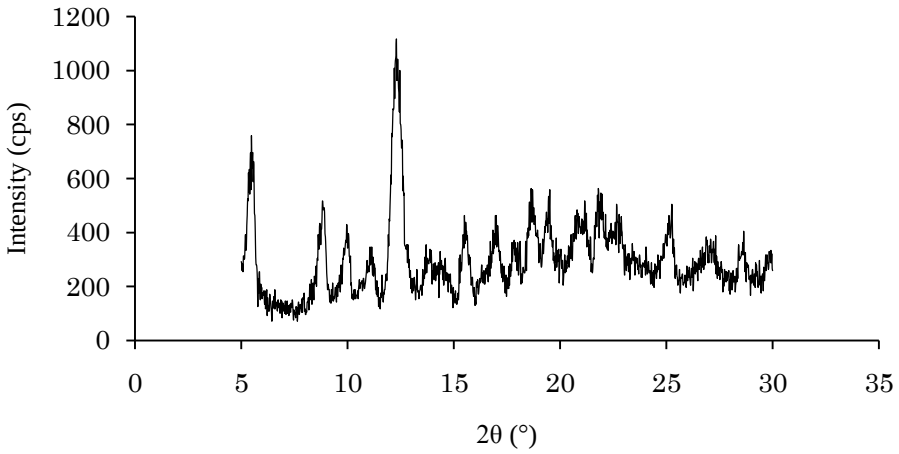

Figure 4: XRPD pattern for PTX.

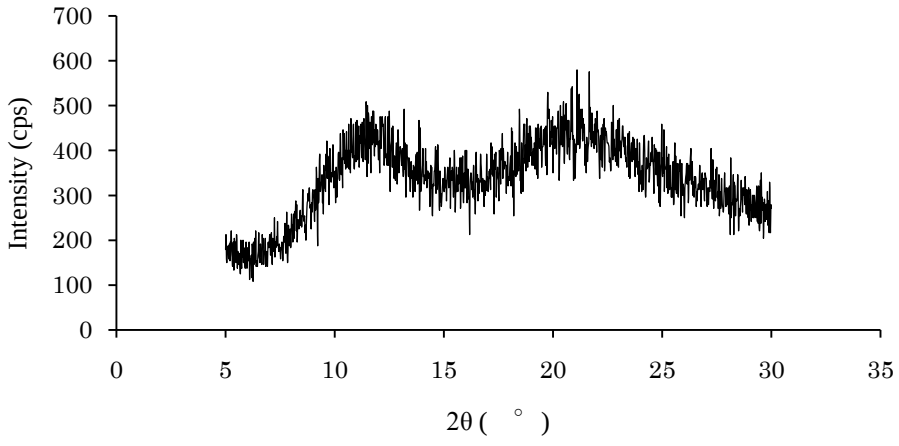

Figure 5: XRPD pattern for PVP.

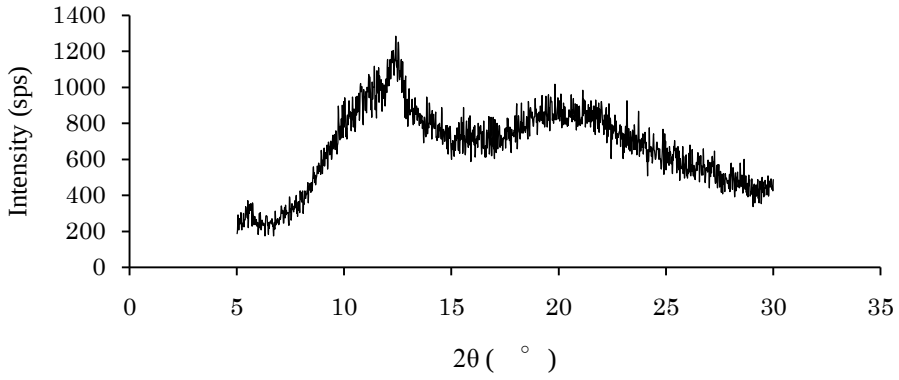

Figure 6: XRPD pattern for the PTX and PVP mixture.

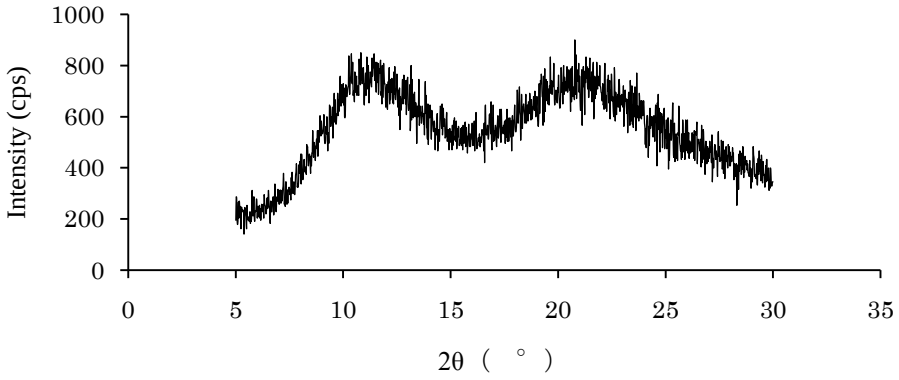

Figure 7: XRPD pattern for the PTX amorphization using PVP.

Dissolution testing

Photographs of the dissolution testing result for each powder are shown in Fig. 8. A is the solution of PTX, B is that of the mixture of PTX and PVP, and C is that of PTX amorphization using PVP. White powder remained in solutions A and B, whereas the white powder in solution C was almost dissolved. These results showed that the solubility of amorphous PTX–PVP improved compared with that of native PTX.

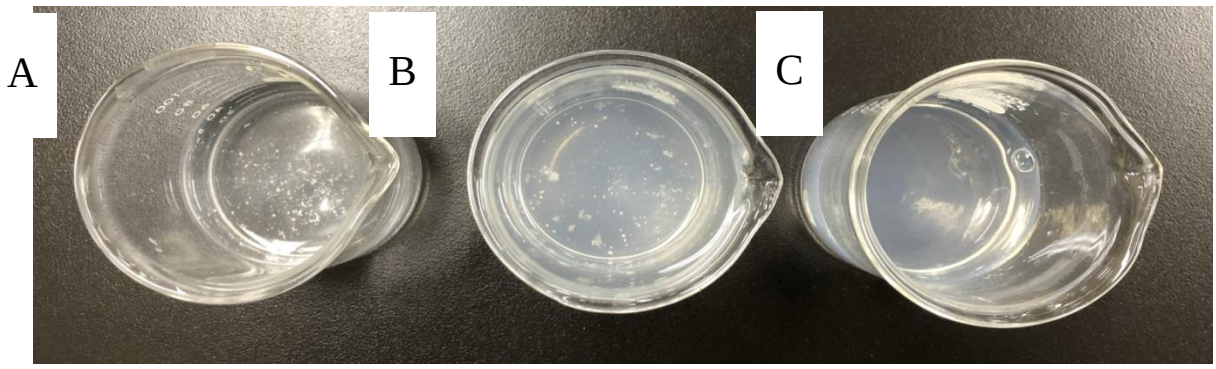

Figure 8: Photographs of the dissolution testing results for each powder.

A: Solution of PTX.

B: Solution of the PTX and PVP mixture.

C: Solution of the PTX amorphization using PVP.

The solubility improvement demonstrates amorphization of PTX, but whether this amorphous form of PTX–PVP is absorbed in the body remains to be clarified in vivo.

One of the problems encountered was the low solubility of PTX in water, which explained why PTX was solubilized initially in ethanol and cremophor EL. However, while this solution showed positive clinical results, long-term exposure to elevated levels of the cremophor EL surfactant required for PTX administration caused undesirable side effects, such as hypersensitivity reactions [23]. The slow infusion of PTX for three hours to reduce those side effects resulted in great inconvenience.

The amorphous solid dispersion approach employed in the present study can be used to improve the solubility of many insoluble drugs, resulting in greater convenience to patients.

4. Conclusion

We report a suitable amorphous solid dispersion technique for improvement of PTX solubility using PVP as a hydrophilic carrier. The formulation of PTX known as Taxol® employs a mixture of cremophor EL and dehydrated ethanol. However, PTX in the present study could be dissolved without cremophor EL. Solubility, one of the major problem associated with most of the new chemical entities, can be reasonably addressed by drug amorphization.

References

1. E.K. Rowinsky, L.A. Cazenave, R.C. Donehower. *J. Natl. Cancer Inst.* 1990, *Vol 82 (15)*, pp1247-1259.

2. M.C. Wani, H.L. Taylor, M.E. Wall, P. Coggon, A.T. Mcphail. *J.Am. Chem. Soc.* 1971, *Vol 93 (9),* pp 2325-2327.

3. R.C. Alves, R.P. Fernandes, J.O. Eloy, H.R.N. Salgado, M. Chorilli. *Crit Rev Anal Chem.* 2018, Vol 48(2), pp110-118.

4. D. G. I. Kingston. *Phytochemistry.* 2007, *Vol 68 (14),* pp1844–1854.

5. J. Szebeni, F.M. Muggia, C.R. Alving. *J. Natl. Cancer Inst*. 1998, *Vol 90 (4),* pp300-306.

6. A. Moreno-Aspitia, E.A. Perez. *Future Oncol*. 2005, *Vol 1(6),* pp755-62.

7. E.R. Gardner, W.L. Dahut, C.D. Scripture. *Clin Cancer Res.* 2008, *Vol 14,* pp4200-4205.

8. M.N. Kundranda, J. Niu. *Drug Des Devel Ther.* 2015, *Vol 24(9),* pp3767-3777.

9. K.Y. Yang, A.M. Yousaf, D.H. Hwang. *Int. J. Nanomed.*2013, *Vol 8,* pp3333-3343.

10. C. Goddeeris, J. Coacci, G. Vanden Mooter. *Eur. J. Pharm. Biopharm.* 2007, *Vol 66,* pp173-181.

11. C. Leuner, J. Dressman. *Eur. J. Pharm. Biopharm.*2000, *Vol 50,* pp47-60.

12. M. Perrut, J. Jung, F. Leboeuf. *Int. J. Pharm.* 2005, *Vol 288,* pp3-10.

13. J.A. Rogers, A.J. Anderson. *Pharm Acta Helv.* 1982, *Vol 57,* pp276-281.

14. O.N. El-Gazayerly. *Drug Dev Ind Pharm.* 2000, *Vol 26,* pp925-930.

15. S.R. Vippagunta, K.A. Maul, S. Tallavajhala, D.J.W. Grant. *Int J Pharm.* 2002, *Vol 236,* 111-123.

16. G.V. Murali Mohan Babu, C.H.D.S. Prasad, K.V. Ramana Murthy. *Int J Pharm.* 2002, *Vol 234,* pp1-17.

17. S. Okonogi, E. Yonemochi, T. Oguchi, S. Puttipipatkhachorn, K. Yamamoto. *Drug Dev Ind Pharm.* 1997, *Vol 23*, pp1115-1121.

18. S. Torrado, S. Torrado, J.J. Torrado, R. Cadorniga. *Int J Pharm.*1996, *Vol 140*, pp247-250.

19. M.C. Tros de Ilarduya, C. Martín, M.M. Goñi, M.C. Martinez-Ohárriz. *Drug Dev Ind Pharm.* 1998, *Vol 24*, pp295-300.

20. M.T. Sheu, C.M. Yeh, T.D. Sokoloski. *Int J Pharm.* 1994, Vol 103, pp137-146.

21. K. Yamashita, T. Nakate, K.A. Okimoto. *Int J Pharm.* 2003, Vol 267, pp79-91.

22. M.T. Marin, M. V. Margarit, G.E. Salcedo GE. *Farmaco.* 2002, *Vol 57*, pp723-727.

23. D.G. I. Kingston, D. G. I. *Phytochemistry* 2007, Vol 68 (14), pp1844-1854.

Corresponding Author:

M.Katsuki*,

Email: m-katsuki@daiichi-cps.ac.jp