Acta Pharm. **59** (2009) 453–461
10.2478/v10007-009-0037-4

Short communication

Physicochemical characterization of solid dispersion systems of tadalafil with poloxamer 407

VIKRANT VYAS
PANKAJKUMAR SANCHETI
POONAM KAREKAR
MANALI SHAH
YOGESH PORE*

Department of Pharmaceutical Chemistry Government College of Pharmacy, Karad Maharashtra-415124, India

Accepted Semptember 14, 2009

Dissolution behaviour of a poorly water-soluble drug, tadalafil, from its solid dispersion systems with poloxamer 407 has been investigated. Solid dispersion systems of tadalafil were prepared with poloxamer 407 in 1:0.5, 1:1.5 and 1:2.5 ratios using the melting method. Characterization of binary systems with FTIR and XRPD studies demonstrated the presence of strong hydrogen bonding interactions, a significant decrease in crystallinity and the possibility of existence of amorphous entities of the drug. In the binary systems tested, 1:0.5 proportion of tadalafil/poloxamer 407 showed rapid dissolution of tadalafil (DE_{30} 70.9 ± 3.6 %). In contrast, higher proportions of poloxamer 407 (1:1.5 and 1:2.5) offered no advantage towards dissolution enhancement of the drug, indicating altered rheological characteristics of the polymer at its higher concentration, which might have retarded the release rate of tadalafil.

Keywords: tadalafil, solid dispersion, poloxamer 407, dissolution

Tadalafil (Fig. 1) is a recently approved phosphodiesterase-5 inhibitor indicated in the treatment of erectile dysfunction (1). It is a selective, potent and reversible competitive inhibitor of the enzyme phosphodiesterase-5 (PDE5), which causes inactivation of cyclic guanosine monophosphate (cGMP) (2). Due to longer duration of its action (approximately 36 hours) and minimum potential to cause vision abnormalities, tadalafil has gained wide clinical acceptance. However, it has very low aqueous solubility (practically insoluble), which leads to its poor dissolution in the gastrointestinal tract, resulting in variable bioavailability. Polymorphism may be the major cause of low aqueous solubility of tadalafil. Poor bioavailability often results in limited or irreproducible clinical response of the drug. It was therefore undertaken to develop effective methods for improvement of the dissolution rate of tadalafil.

Many methods have been reported for the enhancement of aqueous solubility and dissolution rate of poorly water-soluble drugs, including the use of surfactants (3), in-

* Correspondence; e-mail: yogeshvpore@rediffmail.com

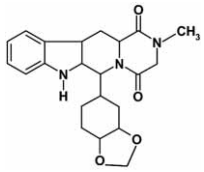

Fig. 1. Chemical structure of tadalafil.

clusion complexation (4), use of polymorphs (5) and solid dispersion (6). In an attempt to improve the dissolution profile of tadalafil, a solid dispersion technique has been employed in this study.

Drug solubilization from solid dispersion systems is mainly due to particle size reduction, increased surface area, reduction in crystallinity and increased wettability by the surrounding hydrophilic carriers that improves the dissolution rate (7).

Pluronic or poloxamer block copolymers have been exploited in pharmaceutical formulations for solubilization of poorly water-soluble drugs (8). Poloxamer consists of a hydrophilic corona (ethylene oxide, EO) and hydrophobic core (polypropylene oxide, PO) blocks arranged in a triblock structure resulting in an amphiphilic structure, characterized by hydrophilic-lipophilic balance (HLB) values (9). Owing to their low melting point, they are suitable for the melt granulation technique in solid dispersions. Their ability to self-aggregate, thereby forming micelles and liquid crystalline phases, and greater hydrophilicity is another advantage for the solubilization of poorly water-soluble drugs. For drug delivery purposes, hydrophobic drugs may be solubilized within the core of the micelle or conjugated to the micelle-forming polymer (10). These amphiphilic co-polymers are available in different grades as poloxamer 188 and poloxamer 407.

This work was aimed to enhance the dissolution rate of tadalafil *via* the solid dispersion technique using poloxamer 407 as a hydrophilic carrier. Solid dispersion systems of tadalafil were prepared with poloxamer 407 in 1:0.5, 1:1.5 and 1:2.5 ratios using the melting technique while a physical mixture was prepared in 1:2.5 ratios for comparison. Different ratios of the polymer were randomly selected. Fourier transform infrared spectroscopy (FTIR) and X-ray powder diffractometry (XRPD) were used to characterize the solid state properties of pure tadalafil and its solid dispersion systems. All formulations, including pure tadalafil, were further evaluated for dissolution performance.

EXPERIMENTAL

Materials

Tadalafil was supplied by Aurobindo Pharma Ltd., India, as a gift sample. Lutrol (poloxamer 407) was a gift sample from Signet Chem Lab, India. All the reagents were of analytical grade. Doubly distilled water was used throughout the experiment.

Preparation of physical mixture

Physical mixture was prepared by co-grinding tadalafil and poloxamer 407 in a mortar in the 1:2.5 ratio (tadalafil/polymer).

Preparation of solid dispersion systems

Solid dispersions (SDs) of tadalafil were prepared by the melting method. Poloxamer was melted at 60 °C. Tadalafil was added to the molten polymer, mixed well and cooled to room temperature to obtain a solid mass. The solidified mass was crushed and passed through an 80-μm aperture sieve. The resulting solid dispersion was stored in a desiccator until use.

Fourier transform infrared spectroscopy (FTIR)

Infrared spectra were recorded on a Perkin-Elmer Spectrum-one FTIR spectrometer (Shelton, USA) using KBr disks. The scanning range was 4000 to 400 cm^{-1}.

X-ray powder diffractometry (XRPD)

The XRPD patterns of pure tadalafil, poloxamer 407 and solid dispersions were recorded using a Philips Analytic X-Ray – PW 3710 (Philips, The Netherlands) diffractometer with tube anode Cu over the 5–70°/2θ interval at a scanning speed of 2° min^{-1}. The generator tension (voltage) and generator current were kept at 40 kV and 30 mA, respectively.

Drug content

Drug content was determined by dissolving solid dispersion equivalent to 5 mg of the drug in a small quantity of dimethylformamide (DMF) and kept in an ultrasonicator for 10 min. The volume was adjusted to 50 mL with 0.5 % sodium lauryl sulphate (SLS). The solution was filtered through Whatman filter paper No. 41, suitably diluted and the absorbance was measured at 292 nm using a double beam UV spectrophotometer (Shimadzu 1700, Japan).

Dissolution studies

The dissolution rate of pure drug and binary systems was measured in 1000 mL of 0.5 % SLS at 50 rpm maintained at 37 ± 0.5 °C in a dissolution apparatus (Model Disso 2000 tablet dissolution test apparatus, Lab India, India) using the paddle method. Tadalafil 20 mg or an equivalent amount of solid dispersion was added to the dissolution medium and samples were withdrawn at appropriate time intervals. The volume of the dissolution medium was adjusted to 1000 mL by replacing it with fresh medium. The samples were immediately filtered through a 0.45-μm membrane filter, suitably diluted and analyzed spectrophotometrically at 292 nm. The results of dissolution studies were statistically analyzed using ANOVA.

RESULTS AND DISCUSSION

Percentage drug content of the formulations was found to be in the range of 98.5 ± 0.4 % (*m*/*m*) (*n* = 3 for each formulation).

FTIR

Fig. 2 shows the FTIR spectra of tadalafil, poloxamer 407, physical mixture and solid dispersion systems. The IR spectrum of tadalafil (Fig. 2a) is characterized by principal absorption peaks at 3328 cm^{-1} (N-H stretch, secondary amine), 3092 cm^{-1} (C-H stretch, aromatic), 2905 cm^{-1} (C-H stretch, aliphatic CH_3 *sym*), 1677 cm^{-1} (C=O amide), 1649 cm^{-1} (C=C aromatic), 1437.62 cm^{-1} (C–N strech), 1041 cm^{-1} (C-O-C stretch *sym*) and 745 cm^{-1} (benzene). The IR spectrum of poloxamer 407 (Fig. 2b) is characterized by principal absorption peaks at 2891 cm^{-1} (C-H stretch aliphatic), 1343 cm^{-1} (in-plane O-H bend) and 1111 cm^{-1} (C-O strech), which were consistent in all binary systems with the drug. The IR spectrum of the physical mixture (Fig. 2c) displayed the superimposition pattern of tadalafil and polymer peaks with decreased peak intensity and little shifting of the peaks. The IR spectrum of 1:0.5 solid dispersion (Fig. 2d) shows disappearance of peaks at 3092 and 2905 cm^{-1} and the presence of all other tadalafil peaks with decreased intensity. In

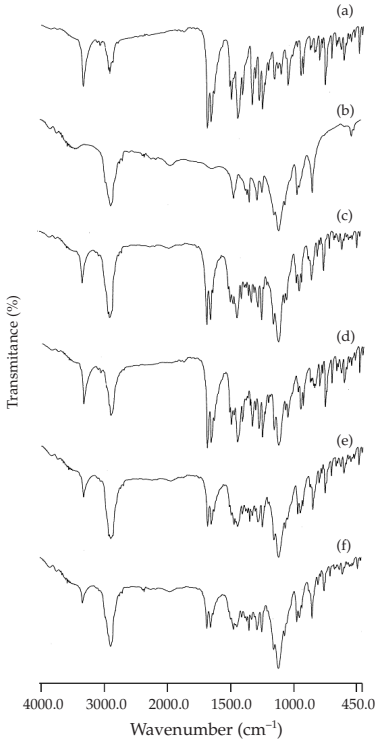

Fig. 2. FTIR spectra of: a) tadalafil, b) poloxamer 407, c) physical mixture, d) 1:0.5 solid dispersion, e) 1:1.5 solid dispersion, f) 1:2.5 solid dispersion.

the IR spectrum of 1:1.5 solid dispersion (Fig. 2e), the peaks at 3092 cm^{-1}, 2905 cm^{-1} and 1041 cm^{-1} are not visible while the peak at 1437.62 cm^{-1} was shifted to 1439.72 cm^{-1}. A gradual decrease in peak intensity was observed with an increase in the proportion of the carrier, as evidenced by smoothing of all other peaks and disappearance of peaks at 3092 cm^{-1}, 2905 cm^{-1}, 1041 cm^{-1} and 1437.62 cm^{-1} of tadalafil in 1:2.5 solid dispersion (Fig. 2f). The peak at 3328 cm^{-1} of NH appeared consistently but was slightly shifted in all binary systems of tadalafil due to hydrogen bonding. All other tadalafil peaks were smoothened, indicating a strong physical interaction of tadalafil with polymer. However, no additional peak was observed in any binary system, indicating absence of any chemical interaction between tadalafil and polymer (11).

XRPD

The XRPD pattern of tadalafil displayed intense and sharp peaks (Fig. 3a), indicating its crystalline nature. Relative decrease in crystallinity (RDC value) was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with those of a reference (pure tadalafil) (12). Tadalafil (Fig. 3a) showed sharp peaks at 7.33, 12.62, 14.47, 14.56, 18.49 and 21.14° (2θ) with peak intensities of 2798, 243, 1043, 1282, 353 and 246, respectively. The crystalline nature of poloxamer 407 is displayed in Fig. 3b. The peak height at 7.335° (2θ) was used to calculate the relative de-

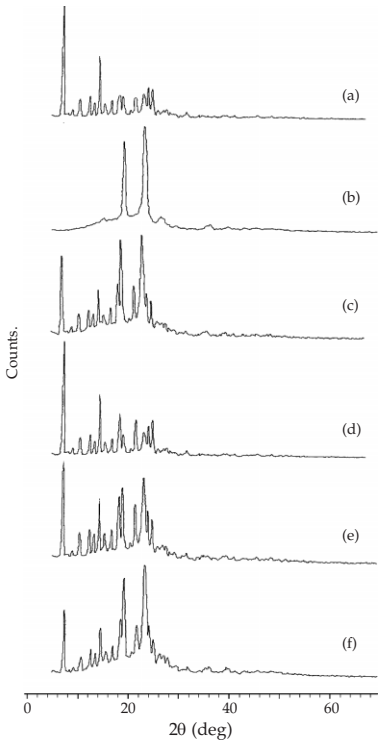

Fig. 3. XRPD patterns of: a) tadalafil, b) poloxamer 407, c) physical mixture, d) 1:0.5 solid dispersion, e) 1:1.5 solid dispersion, f) 1:2.5 solid dispersion.

crease in crystallinity (RDC) of tadalafil in all binary systems (Figs. 3c-f). The XRPD pattern of the physical mixture (Fig. 3c) displayed tadalafil and polymer peaks with a small decrease in the tadalafil peak intensity, indicating reduction in crystallinity (RDC = 0.144). Crystallinity of tadalafil was significantly reduced in the physical mixture, which might be due to higher proportion of the polymer in it (1:2.5). In the diffraction patterns of solid dispersion systems, a gradual decrease in crystallinity was observed with an increase in polymer concentration (Figs. 3d–f). The RDC values for 1:0.5, 1:1.5 and 1:2.5 solid dispersions were 0.278, 0.130 and 0.110, respectively. The peaks of tadalafil at 14.56 and 21.14° disappeared in all solid dispersion systems. The absence of intense peaks in solid dispersions suggested that the drug had lost its crystalline nature and possibly might have been transferred into amorphous form.

Dissolution studies

The dissolution curves of pure tadalafil, physical mixture and solid dispersions in 0.5 % SLS at 37 ± 0.5 °C are shown in Fig. 4. It is evident that the dissolution rate of tadalafil has improved in solid dispersion. Table I shows % drug dissolved in 5 (DP_5), 15 (DP_{15}), 30 (DP_{30}) and 60 min (DP_{60}) for tadalafil and its binary systems with a hydrophilic carrier. The dissolution efficiency values (DE_{30}) in 30 min has been reported and compared statistically.

The binary systems of tadalafil showed faster dissolution than the pure drug. The release of tadalafil within 15 min was 53.3 ± 4.6 % from the physical mixture whereas it was 75.3 ± 3.7, 60.1 ± 4.2 and 52.5 ± 4.4 from 1:0.5, 1:1.5 and 1:2.5 solid dispersions, respectively. However, tadalafil release from the pure drug was only 43.4 ± 4.8 % within 15 min. Thus the physical mixture as well as solid dispersion systems of tadalafil with poloxamer 407 have significantly improved the pure drug dissolution rate (DE_{30}: $p < 0.05$ for PM and 1:2.5 SD; $p < 0.001$ for 1:0.5 SD and $p < 0.01$ for 1:1.5 SD) compared to pure tadalafil. The 1:0.5 ratio of tadalafil/poloxamer solid dispersion has shown the highest dissolution of tadalafil among all the binary systems tested, thus indicating almost complete release of the drug from solid dispersion (DP_{60}: 100.0 ± 3.8 %). However, the release of pure drug was incomplete even in 90 min. It was observed that the higher ratios

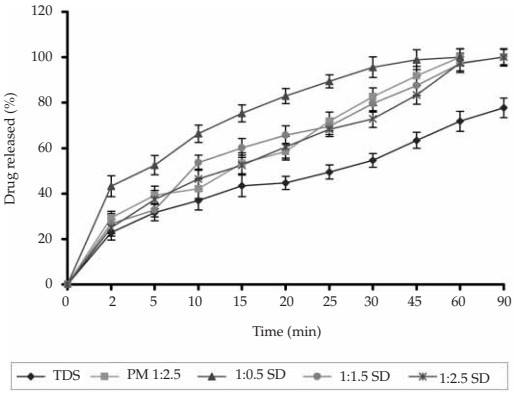

Fig. 4. The dissolution curves of tadalafil-poloxamer 407 systems at 37 ± 0.5 °C (TDS – tadalafil, PM – physical mixture, SD – solid dispersion).

Table I. Dissolution data of pure tadalafil and its binary systems with poloxamer 407 in 0.5 % SLS[a]

System	DP_5 (%)[b]	DP_{15} (%)[b]	DP_{30} (%)[b]	DP_{60} (%)[b]	DE_{30} (%)[b]
Tadalafil	31.6 ± 3.6	43.4 ± 4.8	54.6 ± 3.0	71.8 ± 4.4	39.7 ± 3.5
PM	39.3 ± 4.0	53.3 ± 4.6	82.6 ± 3.9	100.0 ± 3.7	52.2 ± 3.8[c]
1:0.5 SD	52.5 ± 4.2	75.3 ± 3.7	95.6 ± 4.5	100.0 ± 3.8	70.9 ± 3.6[d]
1:1.5 SD	32.7 ± 3.0	60.1 ± 4.2	79.7 ± 3.8	97.2 ± 3.1	54.7 ± 3.6[e]
1:2.5 SD	37.3 ± 4.0	52.5 ± 4.4	72.8 ± 3.7	97.5 ± 4.3	51.1 ± 3.9[c]

[a] Temperature: 37 ± 0.5 °C.
[b] Mean ± SD (n = 3).
PM – Physical mixture, SD – Solid dispersion, DP_5 – DP_{60} – drug dissolved at 5, 15, 30 and 60 min (%), *DE* – dissolution efficiency at 30 min (%).
Significant difference compared to pure tadalafil: [c] $p < 0.05$; [d] $p < 0.001$; [e] $p < 0.01$.

of poloxamer 407 (1:1.5 and 1:2.5) retarded the drug release from their corresponding binary systems even though the drug crystallinity was reduced to a greater extent in these binary systems than in the 1:0.5 solid dispersion. This might be due to the gelling property of poloxamer at higher concentrations (13). It can be concluded from the obtained results that 1:0.5 ratio was found to be superior to other ratios of the polymer and could be considered as a proper choice of the carrier for dissolution enhancement of tadalafil. The dissolution rate increase for the physical mixture (DP_{60}: 100.0 ± 3.7 %) was possibly due to the close contact of the drug with the hydrophilic polymer, brought about by the dry mixing process and higher concentration of polymer. This led to increased wettability and dispersibility of the drug, resulting in increased dissolution rate of tadalafil (14). Although DP_{60} for PM is approaching the value for SD 1:0.5, PM has only improved the extent of tadalafil dissolution. On the other hand, SD 1:0.5 had the enhancing effect on both the rate and extent of tadalafil dissolution. The enhancement of dissolution of tadalafil from PM might be due to higher concentration of the polymer in PM that might have resulted in increased wettability and dispersibility of the drug. Thus higher surfactant property of polymer could be responsible for the increased dissolution rate of tadalafil from PM. Further, *DP*s for PM were very close to the values of 1:1.5 and 1:2.5 SDs even though the crystallinity of the drug was decreased to a higher extent in these SDs (XRPD). The reason lies in the fact that SDs 1:1.5 and 1:2.5 retarded the release rate of the drug. The effect might be due to the property of the polymer to undergo thermoreversible gelling at higher concentration after melting and subsequent cooling during the formulation of solid dispersion systems. However, this effect has not been observed in SD 1:0.5 because of lower concentration of the polymer in this binary system.

The rapid dissolution of tadalafil from solid dispersions may be attributed to the decrease in the drug crystallinity and its molecular and colloidal dispersion in the hydrophilic carrier matrix. As the soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of very fine particles for quick dissolution (15). The poloxamer copolymers exist in solution as unimers but self-assemble into micelles. At concentrations above the critical micelle concentration (*CMC*) unimer molecules aggregate to form micelles. The hydrophobic propylene oxide core of the micells can incorpo-

rate water-insoluble molecules, which results in increased solubility of the drug molecule (9). Besides, higher hydrophilicity and surface property of poloxamer 407, increased wettability and dispersibility and particle size reduction of the drug (9, 11) are also contributing to enhancement of tadalafil dissolution. Higher hydrophilicity and surfactant property of the poloxamer result in greater wetting and increase the surface available to dissolution by reducing interfacial tension between the hydrophobic drug and dissolution medium.

CONCLUSIONS

In the present investigation, poloxamer 407 has improved significantly the dissolution rate of tadalafil. Physical studies demonstrated the absence of chemical interactions between the drug and polymer, a decrease in crystallinity of tadalafil and the possibility of the presence of the amorphous form of tadalafil in solid dispersions systems. Among the ratios used, 1:0.5 ratio of solid dispersion was found to be optimal for its superior performance in dissolution enhancement. This indicated that an increase in the mass fraction of polymer could not offer any advantage for dissolution enhancement. Based on these results, it can be concluded that solid oral dosage forms of tadalafil with poloxamer 407 could be formulated with a high dissolution rate, faster onset of action and improved bioavailability.

Acknowledgements. – The authors are thankful to Shivaji University, Kolhapur, Maharashtra, India, for providing FTIR and XRPD facilities. The authors are very grateful to the Principal, Govt. College of Pharmacy, Karad, Maharashtra, India, for providing laboratory facilities and constant encouragement.

REFERENCES

1. D. A. Hussar, New drugs of 2003, *J. Am. Pharm. Assoc*. **44** (2004) 168–206; DOI: 10.1331/154434504773062627.
2. H. Porst, H. Padma-Nathan, F. Giuliano, G. Anglin, L. Varanese and R. Rosen, Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial, *Urology* **62** (2003) 121–125; DOI: 10.1016/S0090-4295(03)00359-5.
3. H. Schott, L. C. Kwan and S. Feldman, The role of surfactant in the release of very slightly soluble drugs from tablets, *J. Pharm. Sci*. **71** (1982) 1038–1045; DOI: 10.1002/jps.2600710921.
4. F. Veiga, J. J. C. Teixeria-Dias, F. Kedzeierewicz, A. Sousa and P. Maincent, Inclusion complexation of tolbutamide with β-cyclodextrin and hydroxypropyl-β-cyclodextrin, *Int. J. Pharm*. **129** (1996) 63–71; DOI: 10.1016/0378-5173(95)04243-1.
5. J. O. Henck, U. J. Griesser and A. Burger, Polymorphie von Arzneistoffen eine wirtschaftliche Herausforderung?, *Pharm. Ind*. **59** (1997) 165–169.
6. L. Christian and J. Dressman, Improving drug solubility for oral delivery using solid dispersions, *Eur. J. Pharm. Biopharm*. **50** (2000) 47–60; DOI: 10.1016/S0939-6411(00)00076-X.
7. D. Q. M. Craig, The mechanisms of drug release from solid dispersions in water-soluble polymers, *Int. J. Pharm*. **231** (2002) 131–144; DOI: 10.1016/S0378-5173(01)00891-2.

8. M. Newa, K. H. Bhandari, D. X. Li, T. H. Kwon, J. A. Kim, B. K. Yoo, J. S. Woo, W. S. Lyoo, C. S. Yong and H. G. Choi, Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188, *Int. J. Pharm.* **343** (2007) 228–237; DOI: 10.1016/j.ijpharm.2007.05.031.
9. G. Dumortier, J. L. Grossiord, F. Agnely and J. C. Chaumeil, A review of poloxamer 407 pharmaceutical and pharmacological characteristics, *Pharm. Res.* **23** (2006) 2709–2728; DOI: 10.1007/s11095-006-9104-4.
10. D. S. Singhare, S. Khan and P. G. Yeole, Poloxamers: Promising block co-polymers in drug delivery, *Indian J. Pharm.* Sci. **67** (2005) 523–531.
11. J. L. Ford, The current status of solid dispersions, *Pharm. Acta Helv.* **61** (1986) 69–88.
12. J. A. Ryan, Compressed pellet X-ray diffraction monitoring for optimisation of crystallinity in lyophilised solids: imipenem: cilastatin sodium case, *J. Pharm. Sci.* **75** (1986) 805–807; DOI: 10.1002/jps.2600750817.
13. Y. J. Park, C. S. Yong, H. M. Kim, J. D. Rhee, Y. K. Oh, C. K. Kim and H. G. Choi, Effect of sodium chloride on the release, absorption and safety of diclofenac sodium delivered by poloxamer gel, *Int. J. Pharm.* **263** (2003) 105–111; DOI: 10.1016/S0378-5173(03)00362-4.
14. G. Mooter, P. Augustijns, N. Blaton and R. Kinget, Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30, *Int. J. Pharm.* **164** (1998) 67–80; DOI: 10.1016/S0378-5173(97)00401-8.
15. T. Save and P. Venkitachalam, Studies on solid dispersions of nifedipine, *Drug Dev. Ind. Pharm.* **18** (1992) 1663–1679; DOI: 10.3109/03639049209040893.

S A Ž E T A K

Fizikokemijska karakterizacija čvrstih disperzijskih sustava tadalafila s poloksamerom 407

VIKRANT VYAS, PANKAJKUMAR SANCHETI, POONAM KAREKAR, MANALI SHAH i YOGESH PORE

U radu je ispitivano oslobađanje u vodi teško topljivog lijeka tadalafila iz čvrstih disperzijskih sustava. Ti sustavi pripravljeni su s poloksamerom 407 u omjeru lijeka i polimera 1:0,5, 1:1,5 i 1:2,5, koristeći metodu taljenja. Karakterizacija binarnih sustava s FTIR i rendgenskom difrakcijom praha XRD ukazuje na prisutnost snažnih vodikovih veza, značajno smanjenje kristaliničnosti i moguću prisutnost amorfnog lijeka. Iz binarnog sustava tadalafil/poloksamer 1:0,5 oslobađanje ljekovite tvari je brzo (DE_{30} 70,9 ± 3,6 %). Nasuprot tome, iz pripravaka s višim omjerima lijeka i polimera (1:1,5 i 1:2,5) oslobađanje ljekovite tvari nije povećano. Usporavanje oslobađanja tadalafila moglo bi biti posljedicom promjene reoloških svojstava polimera pri višim koncentracijama.

Ključne riječi: tadalafil, čvrsta disperzija, poloksamer 407, oslobađanje

Department of Pharmaceutical Chemistry, Government College of Pharmacy, Karad, Maharashtra-415124, India