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In sight into tadalafil – block copolymer binary solid dispersion: Mechanistic investigation of dissolution enhancement

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ABSTRACT

Tadalafil is a phosphodiesterase-5 inhibitor that is characterized by low solubility and high permeability. Solid dispersion approach represents a promising carrier system for effective enhancement of dissolution and oral bioavailability of poorly soluble drugs. In the present work, novel tadalafil-loaded solid dispersions employing various block copolymers (Pluronics®) were prepared through fusion technique. Their solubility and dissolution properties were compared to the drug alone. In order to elucidate the mechanism of dissolution enhancement, solid state characteristics were investigated using scanning electron microscopy, Fourier transform infrared spectroscopy, differential scanning calorimetry and powder X-ray diffraction. Furthermore, contact angle measurements were carried out.

The sign and magnitude of the thermodynamic parameters indicated spontaneity of solubilization process. The phase solubility studies revealed A_L type of curves for the carriers. Unlike traditional solid dispersion systems, the crystal form of drug in the formulated systems could not be converted to amorphous form. Most of the studied grades showed dissolution improvement vis-à-vis pure drug, with Pluronic F-127 as the most promising carrier. Mathematical modeling of in vitro dissolution data indicated the best fitting with Korsemeyer–Peppas model. Thus, the results demonstrated that tadalafil/Pluronic F-127 solid dispersion system is a direct and feasible technology which represents a potential candidate for delivering a poorly water-soluble drug with enhanced solubility and dissolution.

1. Introduction

Tadalafil is a recently approved phosphodiesterase-5 (PDE5) inhibitor which was officially born in 2000 and then approved by the FDA in 2003, indicated for the treatment of erectile dysfunction. In comparison to other PDE5 inhibitors, it is the most potent and at least 9000 times more selective for PDE5, compared with sildenafil and vardenafil, tadalafil is much less inhibitory for PDE6, consequently, tadalafil has less than 0.1% occurrence of vision abnormalities (Brock et al., 2002; Carson et al., 2005).

Due to its therapeutic window of 36 h (long duration of action) and minimum potential to cause vision abnormalities, tadalafil has gained wide clinical acceptance for the treatment of erectile dysfunction even its difficult-to-treat cases (Coward and Carson, 2008). However, it is absorbed as a low-solubility and high-permeability, or Class II, drug within the FDA biopharmaceuticals classification system (Chavda et al., 2010; Gupta et al., 2002), which leads to its poor dissolution in the gastrointestinal tract, resulting in variable bioavailability (Lobenberg and Amidon, 2000). Tadalafil has the slowest absorption of the available PDE5 inhibitors with a mean of 2 h to reach its maximum concentration (Carson, 2007).

Poor solubility and hence bioavailability often results in limited or irreproducible clinical response of the drug. It was therefore undertaken to develop effective methods for improvement of the solubility and dissolution rate of tadalafil. Based upon its aqueous solubility and dissolution parameters, the drug bioavailability can unambiguously be regarded as limited solely to dissolution (Stegemanna et al., 2007). Various techniques have been used in attempt to improve solubility and dissolution rates of poorly soluble drugs which includes solid dispersion, micronization, lipid based formulations, liquisolid compacts, and complexation (Saharan et al., 2009). The faster release of free drug is thought to be beneficial since, once being administered orally, the quickly released drug may be passively partitioned into the gastrointestinal tract tissues quickly as a result of the favourable concentration gradient resulting into a rapid onset of action and an improved bioavailability. Lately, a few attempts to enhance tadalafil bioavailability have appeared in the literature. Indeed, it was proven that tadalafil dissolution rate could be enhanced by complexation with cyclodextrins (Badr-Eldin et al., 2008), and preparation of stable O/W microemulsion system (Patel and Rajput, 2007).

However, to our knowledge there is a little work done in the field of solid dispersion (SD) of tadalafil. SD has been demonstrated

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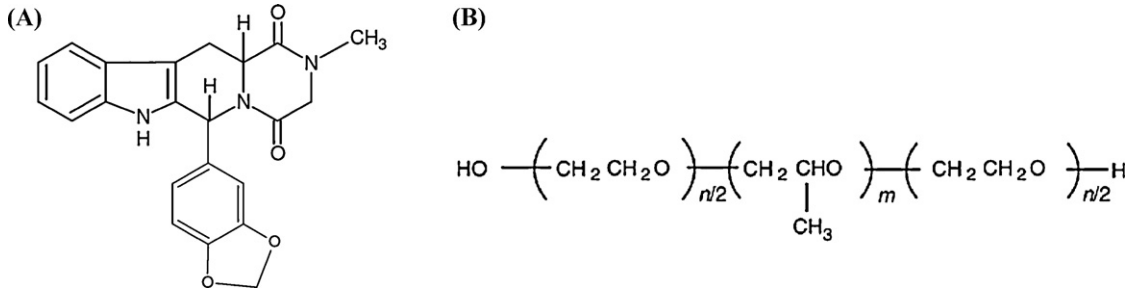

Fig. 1. Molecular structure of tadalafil (A) and Pluronic® block copolymer (B).

as a promising technique for improving the bioavailability of poorly water soluble drugs via the enhancement of their solubility and dissolution rate (Leuner and Dressman, 2000). Although spray drying, co-precipitation, co-evaporation and freeze dying techniques are used for SD manufacturing, costly equipment are required along with complicated procedures. Apart from these techniques, low temperature fusion method has a number of merits, namely; it is a non-solvent technology, therefore it is environmentally friendly, cost effective, represents no stability nor toxicity problems, and can be easily scaled up for commercial purpose (Bhandari et al., 2007).

Pluronics® consist of more than 30 different non-ionic block copolymer surface active agents. These polymers are ABA-type triblock copolymers composed of polyoxyethylene, PEO, (A) and polyoxypropylene, PPO, (B) units (Li et al., 2008). Pluronics® have been widely used as wetting, surface adsorption and solubilizing excipients. In addition, they have been employed to enhance the solubility, dissolution and bioavailability of many poorly soluble drugs among them mefenamic acid (Andrews et al., 2009), coenzyme Q_{10} (Nepal et al., 2010), and felodipine (Kim et al., 2006). Pluronics® in SD formulations have double roles, i.e., one as polymeric carrier and other as surface active agent so it is classified as third generation SD. It has been reported in the literature that the polymeric carrier with surface active properties has additional effect on enhancement of dissolution of poorly water soluble drugs (Passerini et al., 2002).

Therefore, the present study aimed to develop a stable solid dispersion of tadalafil using Pluronics® with significantly enhanced solubility and dissolution rate. In order to evaluate the feasibility of this approach, tadalafil solubility and dissolution studies were performed. Solid-state characterization based on FT-IR spectroscopy, DSC, powder X-ray diffraction and contact angle measurement as well as morphological analysis was carried out to investigate the mechanisms of carrier dissolution enhancement.

2. Materials and methods

2.1. Materials

Tadalafil, assay is 98.5–101% was obtained as a gift from RAMIDA company (Cairo, Egypt) (Fig. 1A). Pluronics®; Pluronic F-127 (PF-127), Pluronic F-68 (PF-68), Pluronic F-77 (PF-77), Pluronic F-38 (PF-38), and Pluronic F-107 (PF-107) copolymers were purchased from Sigma–Aldrich (Steinheim, Switzerland) (Fig. 1B). Potassium dihydrogen phosphate, sodium hydrogen phosphate, sodium chloride and hydrochloric acid (Prolabo, Adwic, El-Nasr Pharmaceutical Co., Egypt). All other solvents and materials used were of analytical grade.

2.2. Phase-solubility studies

Solubility measurements were performed in triplicate using the method reported by Higuchi and Connors (1965). An excess amount of tadalafil was added to the aqueous solutions of Pluronics® in water containing increasing concentrations of various Pluronics® (i.e., 0–20%, w/v). The vials were sealed and shaken at 37 °C for 48 h in a thermostatically controlled water bath and the samples were filtered through a 0.45 μm cellulose nitrate membrane filter. The filtrate was suitably diluted and the concentration in the solution was determined spectrophotometrically at λ_{max} 282 nm.

2.3. Preparation of tadalafil/Pluronic® binary solid dispersions and corresponding physical mixtures

Solid dispersion was prepared by fusion method; Pluronic® of various grades was melted at 70 ± 2 °C for 5 min in a porcelain dish on a water bath under stirring, followed by the addition of drug powder to the to molten carrier and stirring for an additional 5 min until a homogenous dispersion was formed. The dispersion was allowed to solidify at room temperature. After 24 h storage in a desiccator, the solid dispersions were pulverized and sieved; the particle size fraction 100–50 μm was used for all testing.

In addition, control physical mixture of tadalafil/pluronic® prepared by blending them by trituration for 10 min followed with sieving (100 μm).

For optimization of drug and carrier ratio, physical mixtures and SDs of tadalafil and Pluronic F-127 by fusion method were prepared in various weight ratios (1:1, 1:3, 1:5, 1:7, and 1:10, w/w).

2.4. Scanning electron microscopy (SEM)

The surface morphology of tadalafil, tadalafil/PF-127 physical mixture and SD were examined by means of scanning electron microscope (Jeol-JSM-5300 scanning microscope). Electron micrographs of tadalafil solid dispersions were obtained using a scanning electron microscope operating at 25 kV. The samples were mounted on a glass stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation. Micrographs with different magnifications were recorded to study the morphological and surface characteristics of the solid dispersions.

2.5. Fourier transform infrared (FT-IR) spectroscopy

Fourier transform infrared (FT-IR) spectra were obtained using a Perkin Elmer Spectrum RX1 FTIR spectrometer which was employed to characterize the possible interactions between the drug and the carrier in the solid state. Samples of about 2 mg were lightly ground and mixed with IR grade dry potassium bromide and then compressed at 10 tonnes in a hydraulic press for 5 min to form discs. The spectra of tadalafil solid dispersions and physical mixtures were scanned over a frequency range 4000–500 cm^{-1} with a resolution of 4 cm^{-1}.

2.6. Differential scanning calorimetry (DSC)

DSC thermograms were performed with Perkin-Elmer differential calorimeter to determine the DSC thermal traces. Samples of solid dispersions or physical mixtures of drug–carrier were placed in a standard aluminum pan. The instrument was calibrated with indium, dry nitrogen was used as a carrier gas with a flow rate of 25 ml/min and a scan speed of 20 °C/min up to 350 °C was employed. The weight of each sample was 5–10 mg. The main transition temperature (T_C) was determined as the onset temperature of the highest peak. Enthalpy values (ΔH_m) were automatically calculated from the area under the main transition peak.

2.7. Powder X-ray diffraction (PXRD)

The powder X-ray diffractometry patterns were traced at room temperature employing an automated Philips PW 1050/25 diffractometer (Philips, Netherlands) for the samples. Monochromatic Cu Kα radiation was obtained with a Ni-filtration and a system of diverging and scattering slits of 1°.

The data were collected in step scan mode in the region of $4^\circ \leq 2\theta \leq 80^\circ$ with a step size of 0.02° and a dwell time of 0.6 s.

About 200 mg of each sample powder was carefully side-loaded in a sample holder to minimize possible preferential orientation.

2.8. Contact angle measurement

To determine wettability of the substrates, a contact angle was determined. The pellets were prepared for various formulations (400 mg) using tablet press with 5/16″ flat surface punches at 4000 psi pressure and a dwell time of 60 s. A drop of water (approx 2 μL) was placed on the pellet with a micropipette and the contact angle was measured with the help of the digital camera assembly with an overall system magnification of 10×.

2.9. In vitro dissolution studies

The dissolution of pure tadalafil, tadalafil/PF-127 physical mixture and the prepared binary systems were conducted using a USP dissolution tester, apparatus II, in triplicate. The dissolution media were 900 ml of USP simulated gastric fluid (SGF) without pepsin (pH 1.2). A sample equivalent to 10 mg tadalafil of the prepared systems was spread on the surface of the dissolution medium. The stirring speed was 50 rpm, and the temperature was maintained at 37 ± 0.5 °C. At selected time intervals for a period of 120 min, aliquots each of 5 ml were withdrawn from the dissolution medium through a 0.22 μm membrane filter and replaced with an equivalent amount of the fresh dissolution medium. Concentrations of tadalafil were then determined spectrophotometrically.

2.10. Mathematical analysis

2.10.1. Phase solubility studies

The values of apparent stability constant, K_s, between each drug–carrier combination were computed from the phase-solubility profiles (Chen et al., 2004), as described below:

$$K_s = \frac{\text{slope}}{\text{intercept}}(1 - \text{slope}) \tag{1}$$

The values of Gibbs free energy of transfer, $\Delta G^\circ{}_{tr}$, of tadalafil from plain SGF to aqueous solution of the carriers were calculated according to the following relationship:

$$\Delta G^\circ{}_{tr} = -2.303RT\left(\frac{\log S_0}{S_s}\right) \tag{2}$$

where S_0 and S_s are the molar solubility of tadalafil in 1% (w/v) aqueous solution of the carrier and in the plain SGF, respectively. R is the general gas constant while T is absolute temperature (Chen et al., 2004).

2.10.2. In vitro dissolution data

The initial dissolution rate (IDR, % dissolved/min) was computed over the first 5 min of dissolution. Additionally, alternative parameter that describes the dissolution rate is the mean dissolution time (MDT); the most likely time for a molecule to be dissolved from a solid dosage form. Therefore, MDT is the mean time for the drug to dissolve under in vitro dissolution conditions. This is calculated using the following equation:

$$\text{MDT} = \frac{\sum_{j=1}^{n} t_j \Delta M_j}{\sum_{j=1}^{n} t_j \Delta M_j} \tag{3}$$

where j is the sample number, t_j is the midpoint of the jth time period easily calculated with $[t + (t-1)]/2$ and ΔM_j is the additional amount of drug dissolved between t_j and $t-1$.

The mean dissolution rate (MDR) can be calculated according to the following equation:

$$\text{MDR} = \frac{\sum_{j=1}^{n} \Delta M_j / \Delta t}{n} \tag{4}$$

where n is the number of dissolution sample times, Δt is the time at midpoint between t and $t-1$ (easily calculated with $(t + t - 1)/2$) and ΔM_j is the additional amount of drug dissolved between t_j and $t-1$ (Al-Hamidia et al., 2010).

2.10.3. Mathematical models of release kinetics

Kinetics of tadalafil released from the prepared solid dispersions, were examined based on the magnitude of correlation coefficients obtained after application of zero order, first order, Hixson–Crowell cube root, Korsemeyer–Peppas and Higuchi diffusion models employing the following set of equations:

Zero-order kinetic model:

$$M_0 - M_t = k_0 t \tag{5}$$

First-order model:

$$\ln\left(\frac{M_0}{M_t}\right) = k_1 t \tag{6}$$

Higuchi model:

$$M_t = K\sqrt{t} \tag{7}$$

Hixson–Crowell cube root model:

$$(W_0)^{1/3} - (W_t)^{1/3} = k_{1/3} t \tag{8}$$

Korsemeyer–Peppas model:

$$\frac{M_t}{M_\infty} = kt^n \tag{9}$$

where M_0, M_t and M_1 correspond to the drug amount taken at time equal to zero, dissolved at a particular time, t, and at infinite time, respectively. The terms W_0 and W_t refer to the weight of the drug taken initially and at time t. Various other terms viz. k, k_0, k_1, $k_{1/3}$ and k refer to the release kinetic constants obtained from the linear curves of Korsemeyer–Peppas, zero-order, first-order, Hixson–Crowell cube root law and Higuchi model, respectively (Ahuja et al., 2007).

2.10.4. Statistical analysis

Data analysis was carried out with the software package Microsoft Excel, version 2007. Results are expressed as

Table 1
Solubility parameters and values of Gibbs free energy of transfer, ΔG°_{tr}, a thermodynamic parameter of the solubility process and molar solubility of tadalafil in the aqueous solution of various Pluronics® at 37 °C.

Pluronic grade (1%, w/v)	Slope ($\times 10^{-4}$)	Stability constant (ml/g)	r^2	Molar solubility	Gibbs free energy of transfer ΔG°_{tr} (J/mole)
PF-38	3.378	80.933	0.979	0.0185	−420.536
PF-68	3.888	106.998	0.946	0.0167	−196.540
PF-77	2.961	70.484	0.897	0.0154	−10.240
PF-108	4.409	100.131	0.988	0.0222	−833.099
PF-127	**22.057**	**1528.873**	**0.999**	**0.0508**	**−3478.910**

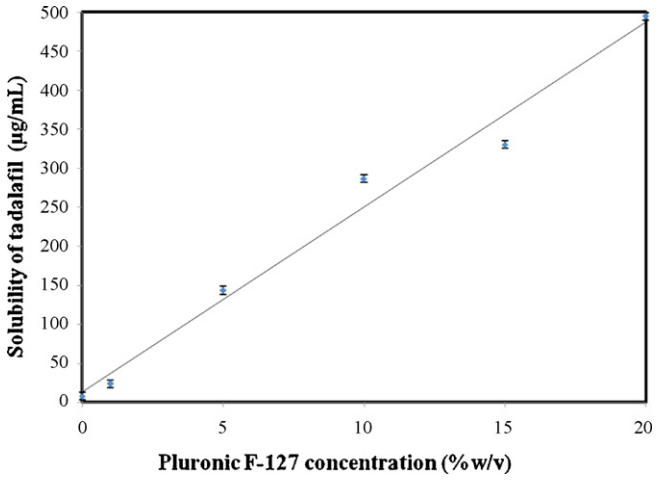

Fig. 2. Phase solubility diagram of tadalafil in aqueous solutions of Pluronic F-127 at 37 °C.

mean ± standard deviation. Student's *t*-test was used for comparison between two samples. $p < 0.05$ was used as a minimal level of significance.

3. Results and discussion

3.1. Feasibility assessment of Pluronic® block copolymers as SD carriers

Surfactants are classified as third generation solid dispersion carriers intended to achieve the highest degree of bioavailability of poorly soluble drugs and to stabilize the solid dispersion. The use of Pluronics® as carriers was shown to be efficient in producing high polymorphic purity and enhanced *in vivo* bioavailability (Vasconcelos et al., 2007). Various Pluronics® grades were screened as tadalafil carriers. Tadalafil aqueous solubility was observed to be 7.72 ± 0.28 µg/ml; therefore, tadalafil can be defined as practically insoluble drug according to USP. Phase solubility parameters showed an increase in drug solubility with different Pluronics®, with r^2 values varying between 0.897 and 0.999. The phase solubility diagram followed an A_L-type system as the computed slopes are less than unity (Higuchi and Connors, 1965) where a linear increase in tadalafil solubility was observed as a function of PF-127 concentration (Fig. 2). The values of the lopes for the various linear curves enlisted in Table 1 indicated the relative solubilizing efficiency of the different carriers. Pluronic F-127 had the maximum solubilizing efficiency, followed by PF-108, PF-77, PF-68, and finally PF-38.

The Gibbs free energy of transfer (ΔG°_{tr}) gives an indication of the process of transfer of tadalafil from pure water to the aqueous solutions of Pluronics®. ΔG°_{tr} values were negative which unequivocally reflecting the spontaneous nature of the drug solubilization process(Damian et al., 2000). The value of ΔG°_{tr} was the lowest for PF-127 illustrating that the process of tadalafil transfer from water to its aqueous solution was the most favourable amongst all Pluronic® grades studied. In addition, the highest value of apparent stability constant, K_s, obtained for PF-127 binary solution revealed a strong binding affinity between tadalafil and the carrier. Accordingly, Pluronic F-127 was chosen as a carrier for the solid dispersion preparation of tadalafil in subsequent investigations.

3.2. Influence of different drug to carrier ratio on solubility and dissolution rate of tadalafil

In order to optimize the carrier ratio, solubility test was carried out. As illustrated in Fig. 3, the physical mixing of Pluronic F-127 with tadalafil even at 1:10 weight ratio did not increase the drug solubility significantly. The critical micelle concentration of PF-127 was determined to be 0.0076% (w/v) at 37 °C (Lee et al., 2008). Hence, the amount of Pluronic F-127 in all the studied physical mixtures was above the critical micelle concentration. Consequently, micelle concentration should be increased in respect to the increase in the PF-127 concentration in the physical mixtures resulted in enhancement of tadalafil solubility. However, tadalafil solubility did not seem to be a function of micellar concentration, providing inability of PF-127 micellar solubilization to dissolve tadalafil. Similar results were observed with coenzyme Q_{10} (Nepal et al., 2010). On the contrary, in solid dispersion formulations, tadalafil solubility increased greatly with increase in proportion of PF-127 up to the weight ratio of 1:7, higher ratio did not significantly increase the drug solubility. At the weight ratios of 1:5 and 1:7, tadalafil solubility from solid dispersions was more than 6 and 7 times higher as compared to that of corresponding physical mixture. These results suggested that the enhancement of tadalafil solubility by PF-127 could not be only explained on the basis of micellar solubilization only, other mechanisms should be involved.

The dissolution behaviour of pure tadalafil and solid dispersions prepared with PF-127 using fusion method is shown in Fig. 4. It is clear that the pure tadalafil has the lowest dissolution rate and all the studied solid dispersion formulations had a higher dissolution rate where the fastest dissolution rate was obtained for the sample when the ratio of tadalafil: PF-127 was 1:5 (w/w). As the contribution of carrier was increased from 1:5 to 1:7 a remarkable reduction in drug dissolution occurred. This indicated that the ratio of drug to carrier in the solid dispersion was one of the main parameters controlling the performance of this solid dispersion formulation, and a direct relationship between the amount of carrier and tadalafil dissolution rate could not be established.

On the other hand, if the percentage of the carrier is too high, this can lead to the complete absence of crystallinity of the drug and thereby enormous increases in the solubility and release rate of the drug (Leuner and Dressman, 2000). This is not the case in the present study as when the contribution of carrier was increased the dissolution rate decreased. In turn, this could be attributed to changes in the structure of PF-127 and formation of a more viscous diffusion layer during the dissolution (Park et al., 2003).

To facilitate comparison between free drug, solid dispersion and physical mixture, IDR, MDT and MDR were calculated (Table 2). The results clearly show that the highest dissolution efficiency belongs

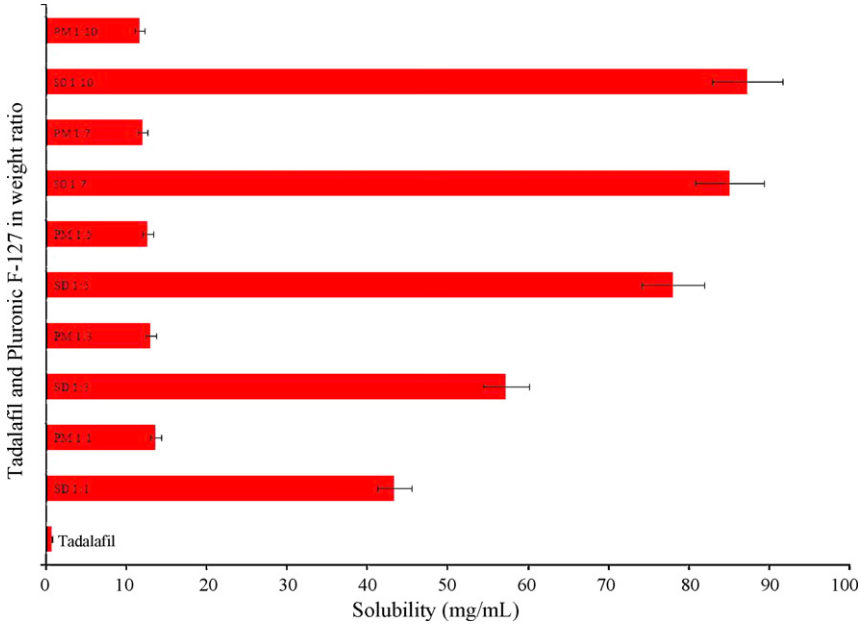

Fig. 3. Comparison of tadalafil solubility in free form, physical mixture and solid dispersions with Pluronic F-127 at various weight ratios (mean ± SD, $n = 3$).

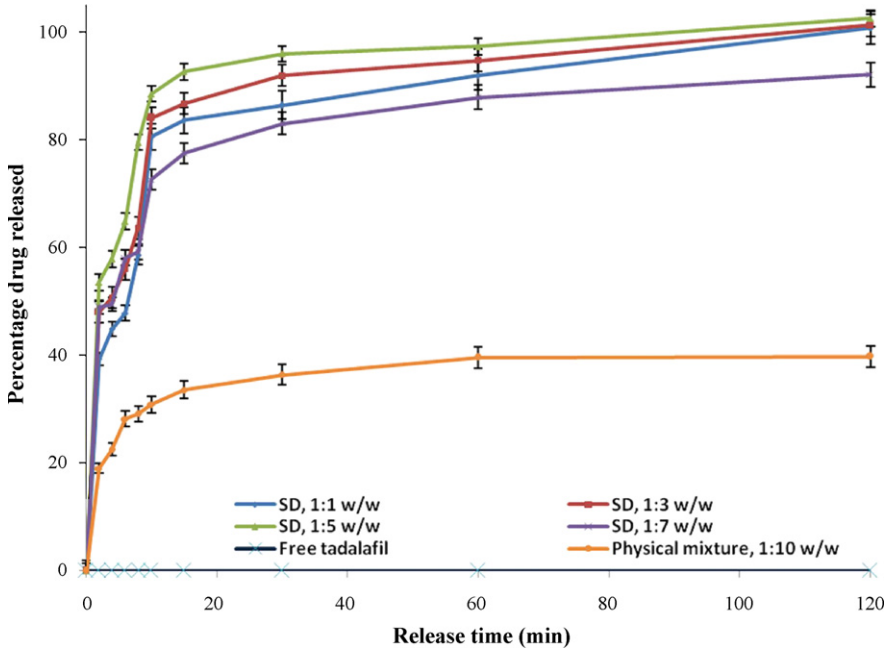

Fig. 4. In vitro dissolution profiles of tadalafil, tadalafil/Pluronic F-127 solid dispersions, and their physical mixture, into stimulated gastric fluid at 37 °C.

Table 2
Dissolution parameters of tadalafil/Pluronic F-127 solid dispersion prepared by fusion method.

Formulation	Dissolution parameters					
	Q_5[a]	Q_{10}[a]	Q_{30}[a]	IDR[b]	MDT[b]	MDR[b]
Free tadalafil	0.00	0.00	0.00	0.00	>100	0.00
Physical mixture (1:7)[c]	25.430	30.870	36.420	4.690	19.880	1.670
Solid dispersion (1:1)[c]	45.430	80.750	89.590	7.970	16.160	3.100
Solid dispersion (1:3)[c]	53.160	83.670	94.860	9.330	12.860	4.370
Solid dispersion (1:5)[c]	60.90	88.050	95.830	10.800	10.100	4.950
Solid dispersion (1:7)[c]	53.220	72.970	82.700	9.670	20.120	4.210

[a] Q: percent drug released at 5, 10, and 30 min.
[b] IDR, MDT, and MDR: initial dissolution rate, mean dissolution time, and mean dissolution rate, respectively.
[c] Numbers represent the weight/weight ratio.

to the SD sample prepared with the ratio of drug to carrier 1:5. The initial dissolution rate during the first 5 min was illustrated in Table 2. From these values, release rates of tadalafil were always higher from the solid dispersions compared with pure drug or the physical mixture, with the 1:5 weight ratios providing a 10-fold increase in the initial dissolution rate. This fast initial rate for the SD is attributable to the hydrogen bonding between tadalafil and PF-127, which breaks relatively easily during dissolution compared with pure drug.

For the SD composition, two mechanisms operate sequentially and explain the biphasic release pattern of this system; initial rapid release results from the molecularly distributed drug followed by release of the remaining microcrystalline drug (Newa et al., 2007). Dissolution from the physical mixture showed only a 4-

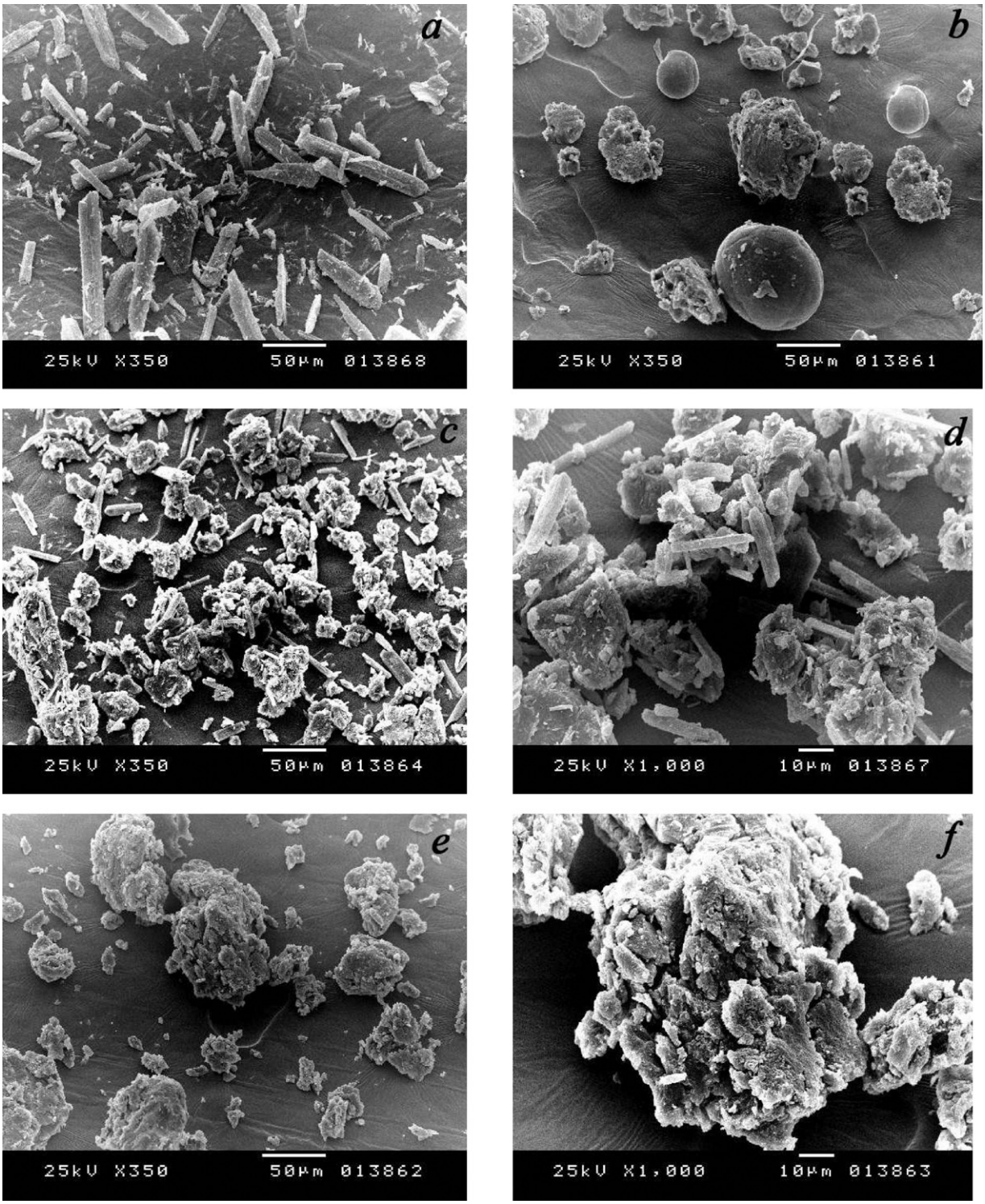

Fig. 5. Scanning electron photomicrographs of tadalafil/Pluronic F-127 solid dispersion prepared by fusion method: (a) free tadalafil, (b) pure Pluronic F-127, (c and d) tadalafil/Pluronic F-127 physical mixture in ratio of 1:5 (w/w) at different magnification powers, and (e and f) tadalafil/Pluronic F-127 solid dispersion in ratio of 1:5 (w/w) at different magnification powers.

fold improvement in the initial release rate of tadalafil. This result is simply explained by solubility studies where tadalafil solubility increased when the equivalent amount of Pluronic® was added to water.

Independent dissolution parameters (IDR, MDR and MDT) usually give an overview of the dissolution rate of a sample throughout the dissolution process, but it does not give an insight into the dissolution rate changes for each time interval. Therefore, Q_5 min, Q_{10} min and Q_{30} min (percent drug dissolved within 5, 10 and 30 min, respectively) were calculated. The results (Table 2) showed that the dissolution rate of pure tadalafil was very low. It can be concluded that all solid dispersions of tadalafil-PF-127 showed considerable enhancement in dissolution rate compared to the physical mixtures. However, the dissolution rate of the physical mixture was higher compared to the pure tadalafil.

The rapid dissolution of tadalafil from solid dispersions may be attributed to 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. In SD system, drug undergoes particle size reduction and the consequent increase in the surface area results in the improved dissolution (Craig, 2002). Moreover, drug solubility and wettability may be increased by surrounding hydrophilic carriers (Craig, 2002).

Pluronic® copolymers exist in solution as unimers but self-assemble into micelles. At concentrations above the critical micelle concentration, unimer molecules aggregate to form micelles. The hydrophobic propylene oxide core of the micelles can incorporate water-insoluble molecules, which results in increased solubility of the drug molecule (Dumortier et al., 2006). Besides, higher hydrophilicity and surface property of PF-127, increased wettability and dispersibility and particle size reduction of the drug are also contributing to enhancement of tadalafil dissolution. Higher hydrophilicity and surfactant property of the PF-127 resulted in greater wetting and increase the surface available to dissolution by reducing interfacial tension between the hydrophobic drug and dissolution medium (Dumortier et al., 2006).

To investigate the mode of release of tadalafil from different solid dispersions, the release data were analyzed using the following mathematical models: zero-order kinetic, first-order kinetic, Hixson–Crowell cube root, Korsemeyer–Peppas and square root of time equation (Higuchi equation).

Based on the correlation coefficient (r^2), the results of kinetic study showed that the best fit was achieved with Korsemeyer–Peppas model for the prepared dispersions, which indicated that drug release mechanism from formulations was the one of diffusion. This behaviour could be attributed to polymer relaxation (Ahuja et al., 2007).

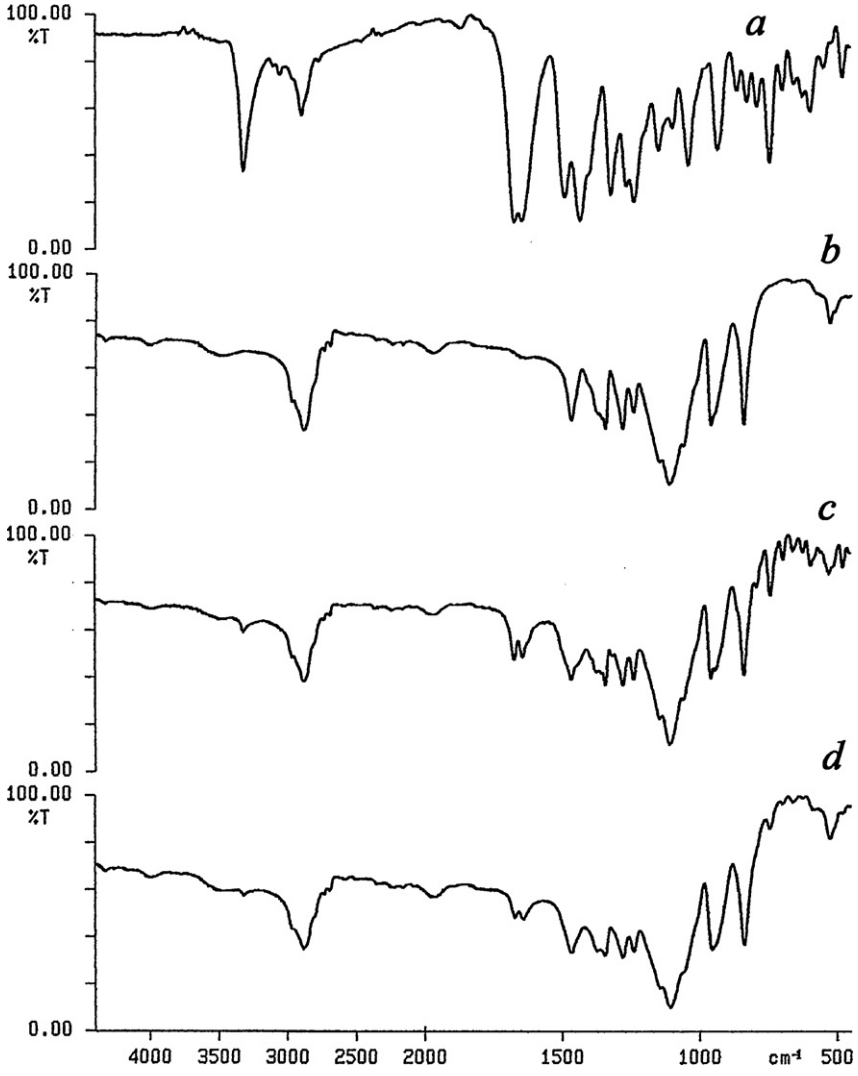

Fig. 6. FT-IR spectra of tadalafil/Pluronic F-127 solid dispersion: (a) free tadalafil, (b) pure Pluronic F-127, (c) tadalafil/Pluronic F-127 physical mixture in ratio of 1:5 (w/w), and (d) tadalafil/Pluronic F-127 solid dispersion in ratio of 1:5 (w/w).

Therefore, the finding shows that inclusion of PF-127 has the benefit of increasing the dissolution rate. In the clinical setting, this means foster the onset of action with the further benefit of improved sexual performance.

The solubility data proves that an improvement in the dissolution rate of solid dispersion cannot be correlated to solubility solely. Therefore, it can be concluded that other parameters such as particle size, morphology of particles, and hydrophilicity of particle surfaces must be responsible for the enhanced dissolution of solid dispersion which is discussed below.

3.3. Investigation of dissolution enhancement mechanisms and solid state characterization

In order to elucidate the mechanisms through which solid dispersions prepared with Pluronic F-127 improved tadalafil dissolution, solid state characterization were carried out.

3.3.1. Morphological and surface analysis of solid dispersions

SEM photomicrographs of free tadalafil, Pluronic F-127, physical mixture of tadalafil/Pluronic F-127 (1:5, w/w) and its solid dispersion were utilized to study their surface morphological characteristics (Fig. 5). Fig. 5(a and b) reveals that pure tadalafil and Pluronic F-127 exist in a smooth-surfaced needles crystalline structures and spherical particles, respectively. The physical mixture of the drug and the carrier at weight ratio of 1:5 showed the presence of drug in the crystalline form along with irregular microparticles of PF-127, which might have been generated due to size reduction process at the time of preparation of the physical mixture (Fig. 5c and d). On the other hand, the photomicrographs of the prepared solid dispersion (Fig. 5e and f) showed the topological changes produced in the carrier particles which seemed to be more porous in nature. The prepared solid dispersion appeared as uniform and homogenous mixed mass with wrinkled surface in which the individual surface properties of both the carrier and the drug were lost during melting and solidification (Fig. 5e and f), and the absence of aggregation of drug crystallites. Similar observations were noted with glibenclamide solid dispersion (Chauhan et al., 2005).

From SEM photomicrographs, it can be speculated that tadalafil existed in very fine crystalline form with reduced particle size, increased surface area and closer contact between the hydrophilic carrier (PF-127) and the drug which may be influential in enhancing drug solubility and dissolution rate (Nepal et al., 2010).

3.3.2. Fourier transform infrared spectroscopy

To study the possibility of the interaction between tadalafil and PF-127 in the solid state, FTIR analysis was carried out. FTIR spectrum of pure tadalafil (Fig. 6a) showed an intense, well-defined characteristic infrared absorption band at 3323.8 cm^{-1} corresponding to the NH stretching vibration of the secondary amine. Two intense absorption bands attributed to the carbonyl stretching vibration were found at 1675.3 cm^{-1} (C=O amide) and 1647.3 cm^{-1} (C=C aromatic). In addition, other sharp bands appeared at 3057.5 cm^{-1} (C–H aromatic stretching), 2900.1 cm^{-1} (C–H aliphatic stretching), 1500–1400 cm^{-1} (C–C aromatic stretching) and 1239 cm^{-1} (C–N stretching).

The Pluronic F-127 infrared spectrum (Fig. 6) is characterized by principle absorption bands at 2888.9 cm^{-1} (C–H aliphatic stretching), 1346.2 cm^{-1}(in-plane O–H bending) and 1110.7 cm^{-1} (C–O stretching).

Fig. 6(c and d) shows the infrared spectra of tadalafil/PF-127 solid dispersion at 1:5 (w/w) ratio and the corresponding physical

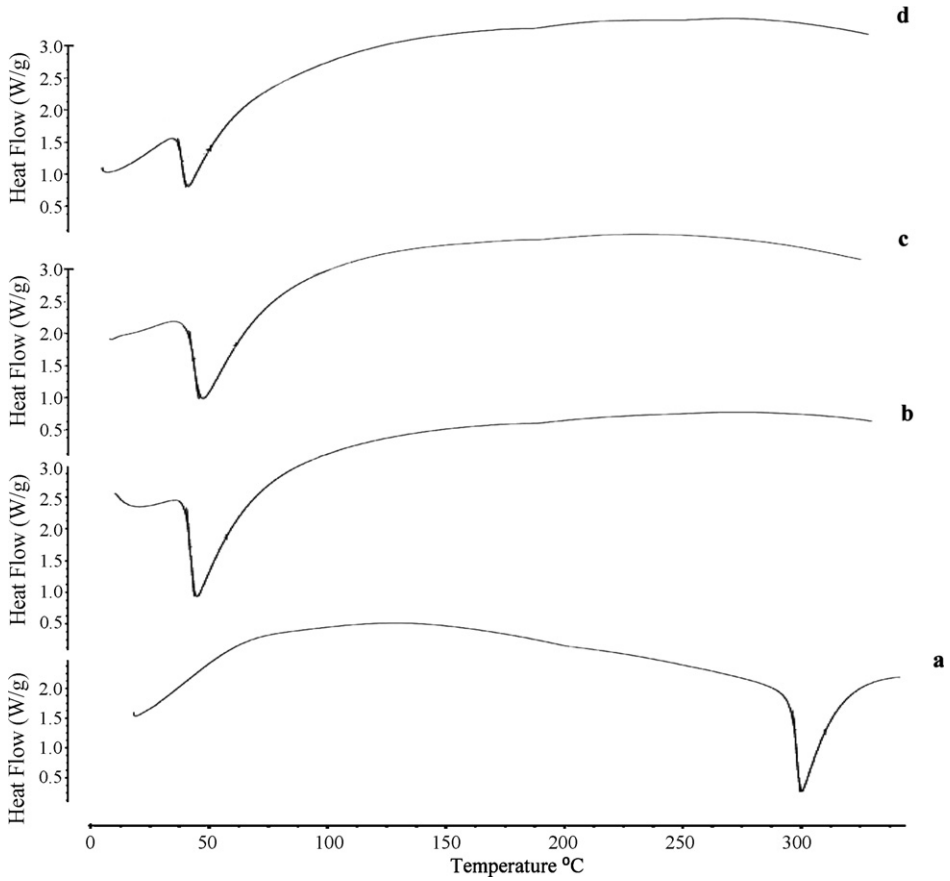

Fig. 7. DSC thermograms of tadalafil/Pluronic F-127 solid dispersion: (a) free tadalafil, (b) pure Pluronic F-127, (c) tadalafil/Pluronic F-127 physical mixture in ratio of 1:5 (w/w), and (d) tadalafil/Pluronic F-127 solid dispersion in ratio of 1:5 (w/w).

Table 3
Intensities at characteristic diffraction angles at 2θ (°) and *d*-values (Å) for tadalafil.

2θ (°)	*d*-value (Å)	Intensity	2θ (°)	*d*-value (Å)	Intensity
6.70	13.180	1168	20.680	4.290	71
8.54	10.330	219	21.150	4.190	1679
9.60	9.200	116	23.670	3.750	1418
10.07	8.760	2368	24.490	3.630	560
12.00	7.360	738	25.510	3.480	139
12.94	6.830	195	26.680	3.330	94
13.98	6.320	696	26.920	3.300	102
15.09	5.860	365	27.320	3.260	112
16.41	5.390	321	27.980	3.180	159
17.87	4.950	1809	28.320	3.140	272
18.92	4.680	101	29.080	3.060	121
20.21	4.380	223	31.440	2.840	126

mixture. The spectra depicted that the physical mixture displayed a superimposition pattern of tadalafil and PF-127 with decreased peaks intensity and the absence of the FTIR major peaks wavenumbers shift of the solid dispersion vis-à-vis its physical mixture revealed the lack of interaction between the drug and the carrier. The presence of the NH stretching vibration of the tadalafil secondary amine in both the solid dispersion and the physical mixture indicated that the drug crystallinity was not totally lost during solid dispersion formation and its attenuated intensities could be due to lower drug content and its slight shifting (from 3323.8 cm^{-1} to 3326.2 cm^{-1}) may be due to hydrogen bonding (Vilhelmsen et al., 2005; Yu et al., 2007).

The absence of significant shift in the peaks positions, retention of the drug characteristics peaks and the nearly equivalent additive spectra of the drug and PF-127 for both the solid dispersion and its physical mixture intensify the absence of interaction in the solid state between tadalafil and PF-127 (Newa et al., 2008).

3.3.3. *Differential scanning calorimetry*

Differential scanning calorimetrical analysis was employed to evaluate the phase of transformation of tadalafil during the formation of solid dispersions via fusion. As reported in Fig. 7, the free tadalafil was characterized by a single, sharp melting endotherm peak of 294.94 °C with an enthalpy of fusion (ΔH) of 112.6 J/g. The DSC curve of tadalafil revealed a crystalline anhydrous substance typical behaviour. DSC trace of Pluronic F-127 showed an endothermic peak at 51.44 °C with an enthalpy of fusion (ΔH) of 74.06 J/g (Fig. 7b).

In the thermal profile of the physical mixture (1:5, w/w), the melting point of tadalafil was hardly detectable (Fig. 7c). This phenomenon can be ascribed to the dissolution of the drug in the melted carriers during program heating, whereas the prepared solid dispersion (1:5, w/w) did not show any melting endotherm of tadalafil. It might be due to the presence of amorphous form of the drug in the SD or the dissolution of crystalline drug into the molten block copolymer carrier (Fig. 7d). Analogous phenomena have been previously reported (Van den Mooter et al., 1998).

Thus, these results ratify the absence of defined interaction between tadalafil and the block copolymer PF-127 as construed by the FT-IR study.

Moreover, on the basis of these thermal analysis results, the crystalline drug could not be detected with DSC in these systems and must be used in combination with other technique analysis.

3.3.4. *Powder X-ray diffraction*

In order to further examine the physical form of the drug in the solidified polymer, SD (1:5, w/w) was investigated using powder X-ray diffraction (Fig. 8). The diffractogram of the solid dispersion vis-à-vis free tadalafil, PF-127 and physical mixture indicates the changes occurred in the crystal structure. The diffraction spectrum of pure tadalafil illustrated that the drug presented in the crystalline form, as demonstrated by numerous distinct peaks. The characteristic peaks for tadalafil and their intensities are presented in Table 3 and Fig. 8(a). The diffractogram of Pluronic F-127 showed two prominent diffraction peaks with the highest intensity at 2θ of 18.71° (4.738 Å) and 22.86° (3.88 Å) (Fig. 8b) so both the drug and the carrier existed in crystalline phases.

The principal peaks of tadalafil and PF-127 were present in their physical mixture (Fig. 8c) and solid dispersion (Fig. 8d) although with lower intensity.

Diffraction peaks of both tadalafil and Pluronic F-127 were sharp, and no amorphous halo was observed, indicating negligible amorphous content and high crystallinity of both components. This may be due to the fact that tadalafil may have either converted to a metastable amorphous form or may have dissolved in the matrix system to form a solid solution, or may exist in a microcrystalline form in the matrix system (Vippagunta et al., 2002).

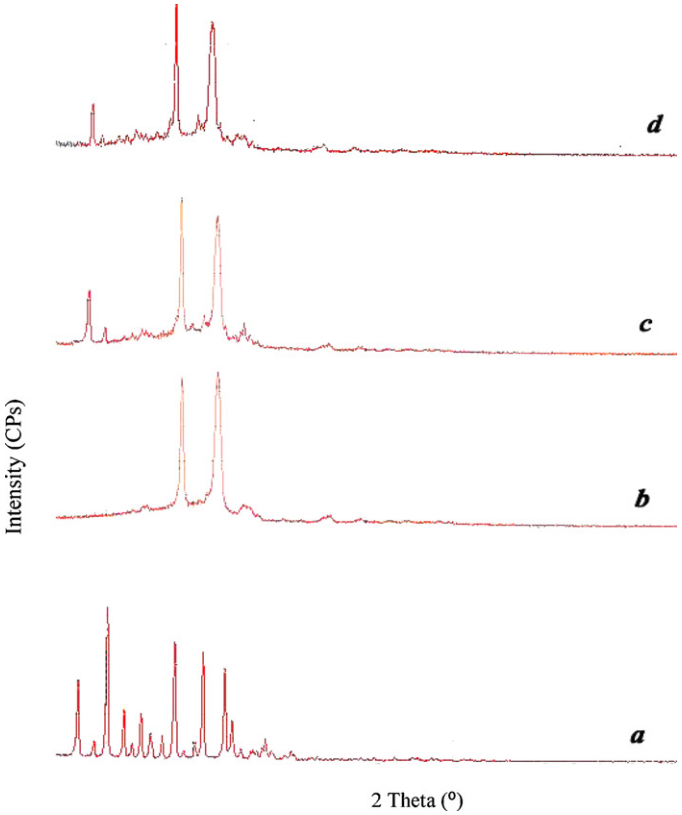

Fig. 8. Powder X-ray diffractograms of tadalafil/Pluronic F-127 solid dispersion: (a) free tadalafil, (b) pure Pluronic F-127, (c) tadalafil/Pluronic F-127 physical mixture in ratio of 1:5 (w/w), and (d) tadalafil/Pluronic F-127 solid dispersion in ratio of 1:5 (w/w).

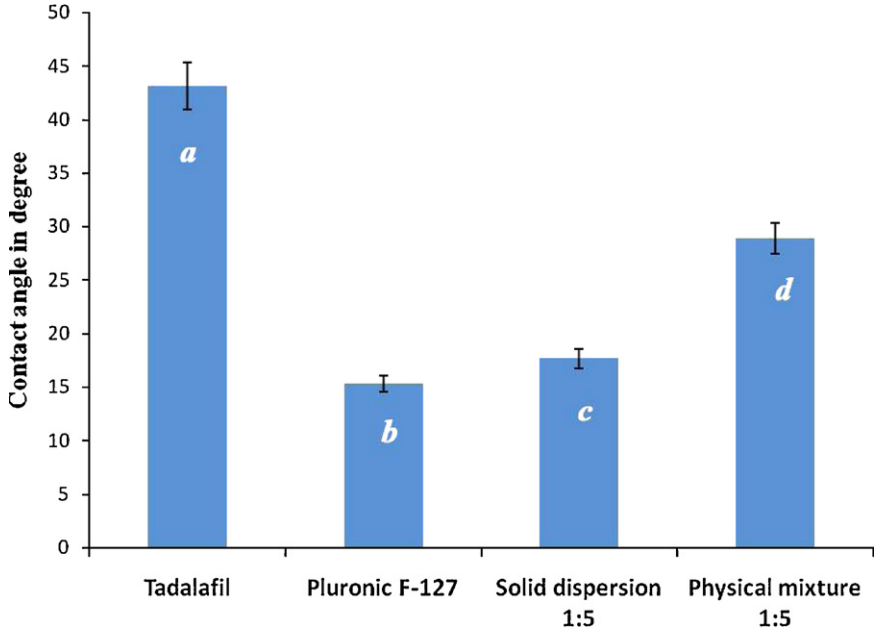

Fig. 9. Contact angle measurement of tadalafil/Pluronic F-127 solid dispersion prepared by fusion method: (a) free tadalafil, (b) pure Pluronic F-127, (c) tadalafil/Pluronic F-127 physical mixture in ratio of 1:5 (w/w), and (d) tadalafil/Pluronic F-127 solid dispersion in ratio of 1:5 (w/w).

No new peaks could be observed, suggesting the absence of interaction between tadalafil and PF-127 (Damian et al., 2000).

3.3.5. Contact angle and wettability studies

The role of pluronic F-127 surface activity in enhancing the dissolution of tadalafil in PF-127 solid dispersion was further supported by evaluating the wetting effect of pluronic F-127. The contact angle results are presented in Fig. 9. The contact angle for the drug was observed to be 43.2°, which indicated the hydrophobic nature of the drug. This hydrophobic nature of the tadalafil was obvious during dissolution testing where the drug particles were floating on the surface of dissolution medium. The physical mixture and solid dispersion showed reduction in the contact angle of the drug in presence of the PF-127. The physical mixture showed 1.5-fold reduction while that of the solid dispersion showed 2.5-fold reduction in contact angle when compared with the pure drug.

The contact angle studies suggest that the PF-127 helped improve wettability of the hydrophobic drug compared to with free drug.

Finally, our studies demonstrated that, the mechanisms involved in tadalafil dissolution rate enhancement are a combination of the following:

1) The reduction in crystalline drug particle size (Newa et al., 2007);
2) Improvement of wetting through intimate contact between a hydrophilic carrier and the drug (Ahuja et al., 2007);
3) The solubilization effect of the carrier (increasing the percentage of carrier enhanced the dissolution rates);
4) Absence of aggregation of drug crystallites (SEM);

In addition to the following minor contributing factors:

5) Improvement of wettability and dispersibility of the drug (contact angle measurement);
6) Dissolution of the drug in the hydrophilic carrier (SEM);
7) Inhibition of fine particle aggregation, but not the conversion of the drug to the amorphous state.

4. Conclusion

In summary, the newly developed solid dispersion show increased solubility and dissolution over the reference formulation containing the free tadalafil.

As already hypothesized from the study, Pluronic F-127 solid dispersion may consequently be a suitable delivery system to improve the biopharmaceutical performance of orally administered tadalafil with low water solubility.

Tadalafil showed increased dissolution rates in presence of Pluronic F-127. Unlike traditional solid dispersion systems, in this particularly proposed solid dispersion the drug retained its crystalline form and PF-127 improved wetting of the drug and minimized agglomeration, which resulted in microcrystalline uniform dispersion of drug in the carrier matrix. In vitro dissolution studies of tadalafil/Pluronic F-127 solid dispersion in the ratio of 1:5 showed that release of tadalafil from solid dispersion is more than that of pure drug when the dissolution was performed in simulated gastric fluid.

Thus, solid dispersion system of tadalafil and Pluronic F-127 would be a potential candidate for delivering a poorly the water-soluble tadalafil with enhanced solubility and stable non convertible crystalline formulation. This system can be used for the oral solid dosage form development in order to be commercialized.

Conflict of interest

The authors report no conflicts of interest.

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