European Journal of Pharmaceutics and Biopharmaceutics 96 (2015) 226–236

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research Paper

Mesophase and size manipulation of itraconazole liquid crystalline nanoparticles produced via quasi nanoemulsion precipitation

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ARTICLE INFO

Article history:
Received 22 May 2015
Revised 3 August 2015
Accepted in revised form 6 August 2015
Available online 8 August 2015

Keywords:
Itraconazole
Liquid crystal
Quasi nanoemulsion
Nematic
Smectic
Poloxamer 407

ABSTRACT

The fabrication of drug nanoparticles (NPs) with process-mediated tunable properties and performances continues to grow rapidly during the last decades. This study investigates the synthesis and phase tuning of nanoparticulate itraconazole (ITR) mesophases using quasi nanoemulsion precipitation from acetone/water systems to seek out an alternative pathway to the nucleation-based NP formation. ITR liquid crystalline (LC) phases were formed and nematic–smectic mesomorphism was achieved via controlling solvent:antisolvent temperature difference ($\Delta T_{S:AS}$). The use of $\Delta T_{S:AS}$ = 49.5 °C was associated with a nematic assembly, while intercalated smectic A layering was observed at $\Delta T_{S:AS}$ = 0 °C, with both phases confined in the nanospheres at room temperature. The quasi emulsion system has not been investigated at the nanoscale to date and in contrary to the microscale, quasi nanoemulsion was observed over the solvent:antisolvent viscosity ratios of 1:7–1:1.4. Poly(acrylic acid) in the solvent phase exhibited a concentration dependent interaction when ITR formed NPs. This nanodroplet-based approach enabled the preparation of a stable ITR nanodispersion using Poloxamer 407 at 80 °C, which was unachievable before using precipitation via nucleation. Findings of this work lay groundwork in terms of rationalised molecular assembly as a tool in designing pharmaceutical LC NPs with tailored properties.

1. Introduction

The advances in drug design have led to a radical change in the development of active pharmaceutical ingredients (APIs), however at a price of dramatically decreasing their biorelevant properties, mainly solubility. Those APIs are estimated to constitute 40% of the currently developed potential drugs, where low bioavailability is the undesirable consequence of the poor solubility. Nanotechnology has been established as a promising pathway to enhance dissolution and solubility of such substances [1]. Itraconazole is an anti-infective drug that suffers from the above drawbacks, however some attempts involving fabrication in the nanoscale have been found to boost its bioavailability [2,3].

While a few reports on amorphous and crystalline ITR nanoparticles (NPs) can be found in the literature, liquid crystalline ITR NPs and, in general, liquid crystalline drug NPs were overlooked [4]. A liquid crystal (LC) is an intermediate state between the crystalline and amorphous states with a combination of residual order and mobility thus known as mesophases [5]. APIs in the LC form have been reported to possess enhanced solubility in comparison with their crystalline counterparts [6]. Almost all types of supramolecular interactions, including van der Walls interaction, hydrogen bonds and π–π interactions, can be observed in LCs [7]. Molecules capable of forming mesophases are known as mesogens and can be classified according to the anisotropy of their shape into rod-like and disc-like [8] with the former exhibiting the highest molecular anisotropy. Thus nanosized liquid crystals possess the combinatorial effect of the nanomaterials' large surface area, the compromised molecular order of mesophases, which is expected to enhance solubility and dissolution, and advantageous stability on comparison to amorphous due to lower Gibbs free energy [9].

ITR molecule is highly anisotropic with a rod like structure (Fig. 1). Nematic and smectic liquid crystalline phases of ITR were previously achieved via controlled cooling of melted crystals [5,10]. However, a nematic phase can easily be misinterpreted as isotropic (amorphous) using X-ray diffraction due to similarity in diffraction patterns of both phases.

Here, we report on tuning the LC phase in ITR NPs through controlling the quasi nano-emulsion precipitation process parameters, especially the solvent to antisolvent temperature difference ($\Delta T_{S:AS}$). The $\Delta T_{S:AS}$ transpired to be a critical parameter associated with the nematic or smectic assembly with both phases, to our surprise, confined in the shell of nanospheres at room temperature which, to

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http://dx.doi.org/10.1016/j.ejpb.2015.08.005
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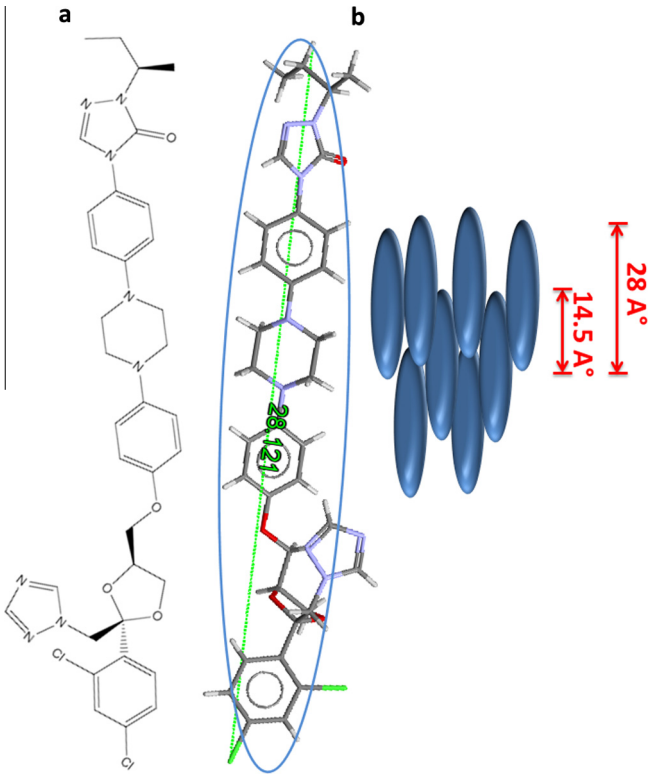

Fig. 1. (a) Chemical structure of ITR (ChemBioDraw). (b) Schematic illustration of ITR molecule (Mercury® 3.5.1) with the molecular arrangement and interplanar spacing in the intercalated smectic A phase.

the best of our knowledge, has not been demonstrated before. The underlying mechanism of ITR NP formation was investigated and the impact of $\Delta T_{S:AS}$, the solvent:antisolvent viscosity ratio (ρ) and functional properties, such as miscibility and possibility of interactions, of the included polymer on the properties of the formed particles were examined. Different polymers were tested including poly(acrylic acid) (PAA), cellulose acetate phthalate (CAP) and Poloxamer 407 (P407), although the focus is mainly on P407 as it demonstrated the capability to markedly improve ITR dissolution [11,12]. The formation of ITR-P407 NPs at elevated temperature adds to the unique achievements of this work since it was reported to be infeasible before [13].

2. Materials and methods

2.1. Materials

Itraconazole (ITR) was a gift from Neuland Laboratories Ltd. (Welding, Hamburg, Germany). Poloxamer 407 (poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol), P407) was purchased from BASF Corp. (Ludwigshafen, Germany). Acetone Chromasolv® HPLC grade was obtained from Sigma–Aldrich (Dorset, UK), while acetonitrile HPLC grade was purchased from Fisher Scientific (Loughborough, UK). Poly(acrylic acid) (PAA), as Carbopol 981 was obtained from BFGoodrich (Brecksville, OH, USA). Ethanol ($\geqslant$99.8%), employed in DVS experiments and cellulose acetate phthalate (CAP) were acquired from Sigma–Aldrich (Dublin, Ireland). All other chemicals were of analytical grade and used as supplied.

2.2. Methods

2.2.1. Determination of solubility of crystalline ITR

The solubility of crystalline ITR in acetone at 50 °C in the presence of P407 at different concentrations (1, 2, 3 and 4 mg/ml) was determined using a high performance liquid chromatography (HPLC) method as carried out before [4].

2.2.2. Preparation of ITR NPs

ITR NPs were prepared as previously described [4] with some modifications and details of experimental conditions are presented in Table 1. The modifications included changing the temperature of the antisolvent phase (water), thus creating temperature gradient ($\Delta T_{S:AS}$). Solvent was acetone. PAA was used to tune the viscosity of the antisolvent phase. CAP was determined to be miscible with ITR based on calculated theoretical miscibility using Flory–Huggins interaction parameters [14].

2.2.3. Dynamic light scattering (DLS) and zeta potential (ZP)

The mean particle size and the polydispersity indices of NPs were measured using a Zetasizer Nano ZS series (Malvern Instruments, UK). The dispersions were placed in DTS1061 clear disposable zeta cells. All measurements were carried out at 25 °C with an equilibration time of 2 min. The analysis was performed in triplicate for each sample and the mean particle diameter along with the polydispersity index was recorded and corrected for viscosity of the continuous phase. Electrophoretic mobility values were measured by laser Doppler velocimetry (LDV) using DTS1061 cells and were converted to zeta potential values.

Table 1
Summary of the precipitation conditions and properties of NPs produced. The solvent:antisolvent (S:AS) v/v ratio was 1:10 in all experiments [4] and the solvent phase was kept at 50 °C. T – temperature, $\Delta T_{S:AS}$ – temperature difference between solvent (S) and antisolvent (AS), ITR – itraconazole, P407 – Pluronic 407, CAP – cellulose acetate phthalate, PAA – poly(acrylic acid) (as Carbopol).

Sample	T_{AS} (°C)	$\Delta T_{S:AS}$ (°C)	ITR concentration (mg/ml)	Polymer concentration in S phase (mg/ml)		Polymer concentration in AS phase (mg/ml)
				P407	CAP	PAA
F1	0.5	49.5	6.4	0	0	0
F2	0.5	49.5	7.9	1	0	0
F3	50	0	6.4	0	0	0
F4	50	0	7.9	1	0	0
F5	80	30	6.4	0	0	0
F6	80	30	7.9	1	0	0
F7	80	30	6.4	0	1	0
F8	80	30	6.4	0	0	0.033
F9	80	30	6.4	0	0	0.05
F10	80	30	6.4	0	0	0.1
F11	80	30	7.9	1	0	0.033
F12	80	30	6.4	0	1	0.033