Food and Chemical Toxicology 119 (2018) 425–429

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Supramolecular strategy for reducing the cardiotoxicity of bedaquiline without compromising its antimycobacterial efficacy

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ARTICLE INFO

Keywords:
Cucurbit[7]uril
Bedaquiline
Supramolecular formulation
Cardiotoxicity
Antimycobacterial

ABSTRACT

Bedaquiline (BDQ) is a newly approved anti-tuberculosis drug in treating multidrug-resistant tuberculosis. However, it has very poor aqueous solubility and several case reports have proposed that BDQ has potential risk of cardiotoxicity to patients. In this present study, we have explored into employing host-guest interactions between a synthetic receptor, cucurbit[7]uril (CB[7]), and BDQ aiming to improve the solubility and reduce the inherent cardiotoxicity of BDQ. HPLC-UV test on the solubility of BDQ in the absence and in the presence of increasing concentrations of CB[7] suggested a host-dependent guest-solubility enhancements. Cardiovascular studies using an *in vivo* zebrafish model demonstrated that the cardiotoxicity of BDQ was indeed alleviated upon its complexations by the synthetic receptor. Furthermore, our *in vitro* antibacterial studies suggested that CB[7] formulated BDQ preserved its antimycobacterial efficacy against *Mycobacterium smegmatis*. Therefore, CB[7] may become a suitable pharmaceutical excipient in formulating BDQ for improving its physiochemical properties (such as solubility), and for alleviating its side effects (such as cardiotoxicity), while the antimycobacterial efficacy of BDQ may be well maintained.

1. Introduction

Tuberculosis (TB) is a major threat to global health (WHO, 2016). Multiple drug-resistant tuberculosis (MDR-TB) is a form of TB infection caused by *Mycobacterium tuberculosis* that is resistant to treatment with at least two of the first-line drugs (WHO, 2016). Bedaquiline (BDQ, Fig. 1a) is a newly developed medicine for the treatment of MDR-TB, which is a long-awaited agent for anti-TB in more than forty years; both its action mechanism and structure are unique to the existing first-line regimens. BDQ is a first-in-class drug of diarylquinoline, by binding to the subunit c of ATP synthase, which is crucial for generating energy in mycobacteria, it suppresses mycobacterial energy metabolism (Andries and Guillemont, 2005; Haagsma et al., 2011). However, a black-box warning was issued in 2012 by the United States Food and Drug Administration for increased mortality and cardiotoxicity, as it may cause heart arrhythmias by prolonging the QT interval (SIRTURO, 2017). Moreover, BDQ has very poor intrinsic aqueous solubility. It is defined to be "very slightly soluble (VSS) in 1M HCl" by the European Medicines Agency (EMA). Some believed that the high lipophillicity of BDQ is responsible for the cardiotoxicity caused (Tong et al., 2017). And less lipophilic analogues have been synthesized and investigated with an attempt to resolve the toxic side effects while maintaining the promising efficacy of BDQ for the treatment of TB (Priebbenow et al., 2016). However, the chemical syntheses of new analogues are usually laborious and the efficacy can be challenging to retain. Therefore, these concerns inspired us to adapt a novel, facile supramolecular approach to formulate BDQ with a synthetic macrocyclic receptor.

Cucurbit[7]uril (CB[7], Fig. 1b), a synthetic macrocyclic receptor, is the most studied member in the cucurbit[n]uril (CB[*n*], n = 5–8, 10–14) family with regards to biomedical applications due to its superior water solubility and appropriate size to accommodate a variety of guest molecules of biomedical interest (Yin and Wang, 2017). Over the years, numerous investigations have demonstrated that upon complexation by CB[7], the solubility and stability of a variety of guest molecules were improved (Kuok et al., 2017). In addition, upon encapsulation by CB[7], the toxic side effects of guest drug molecules are often reduced and the therapeutic efficacies could be maintained or even improved (Kuok et al., 2017). For instance, a study reported the

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https://doi.org/10.1016/j.fct.2017.12.022
Received 26 November 2017; Received in revised form 13 December 2017; Accepted 15 December 2017
Available online 16 December 2017
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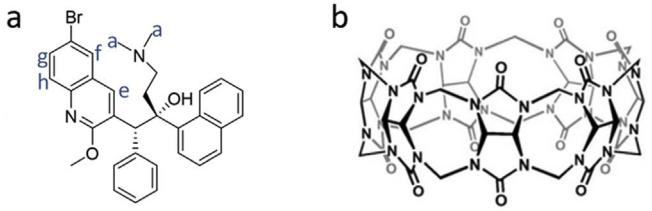

Fig. 1. Chemical structures of BDQ (a) and CB[7] (b) with key protons labeled.

non-specific hepatotoxicity of isoniazid, could be potentially reduced by forming host-guest inclusion complex with CB[7] and by altering the amount of CB[7], the rate of isoniazid acetylation could be controlled, thus potentially reducing the hepatotoxic effect associated with N-acetylated isoniazid to patients with the fast-acetylator phenotype (Cong et al., 2011). On the other hand, in the presence of CB[7], the solubility of clofazimine, another anti-TB drug, could be improved reaching a concentration of up to approximately 0.53-fold of the maximum solubility of CB[7]. While the antimycobacterial efficacy of clofazimine was maintained with the MIC_{50} in the order of 10^{-6} M towards *Mycobacterium smegmatis* (*MS*), the *in vivo* experiment in zebrafish demonstrated that the cardiotoxicity caused by clofazimine was reduced when formulated with CB[7] (Yew et al., 2017) (Li et al., 2016). Likewise, a recent study established that CB[7] also improved the solubility of sorafenib in an NMR phase solubility analysis, by forming CB[7]-sorafenib complex with $K_a = (2.87 \pm 0.13) \times 10^5\ M^{-1}$. Analysis of zebrafish cardiac function and morphology showed that the complex reduced the cardiotoxicity caused in zebrafish as compared to the free drug, while the therapeutic efficacy was not affected upon complexation by CB[7] shown in *in vitro* anti-angiogenic activity studies (Yang et al., 2017). We have also previously demonstrated that the complexation of a general anesthetic agent by CB[7] reversed its anesthesia effects on a zebrafish model (Chen et al., 2015).

Encouraged by these results, the aim of this research was to investigate the host-guest complexations between CB[7] and BDQ, as well as the potential benefits of such supramolecular formulation on the solubility, nonspecific toxicity, and therapeutic efficacy of the guest drug. This study may provide new insights on novel formulation strategies of MDR-TB drugs.

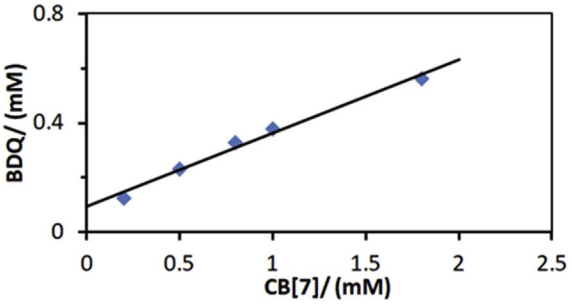

Fig. 3. Phase solubility diagram of BDQ in the presence of increasing concentrations of CB[7] (0.2, 0.5, 0.8, 1.0, 1.6 and 2.0 mM), determined from HPLC-UV chromatogram integrations (the linear fit equation: $y = 0.270\ x + 0.093$, $R^2 = 0.987$).

2. Materials and methods

2.1. Reagents and materials

CB[7] was synthesized according to the reported method (Day et al., 2001). BDQ was purchased from International Laboratory (IL, CA 94080, USA) and used as received. Ammonium acetate, NaCl, KCl, $CaCl_2$, Mg_SO_4, HPLC grade methanol, acetonitrile and all other chemicals were commercially available and purchased from Sigma Aldrich (St. Louis, USA). Ultrapure water was obtained from a Millipore water system (Millipore, Bedford, Massachusetts).

2.2. Nuclear magnetic resonance (NMR) study

^{1}H NMR and COSY NMR spectra were obtained using Bruker 600 MHz NMR spectrometer. Briefly, a solution of BDQ was dissolved in D_2O with minimum amount of DCl, in which different equivalents of CB[7] (0.5 eq, 1.2 eq and 2.2 eq) was added. These samples were sonicated before NMR measurements.

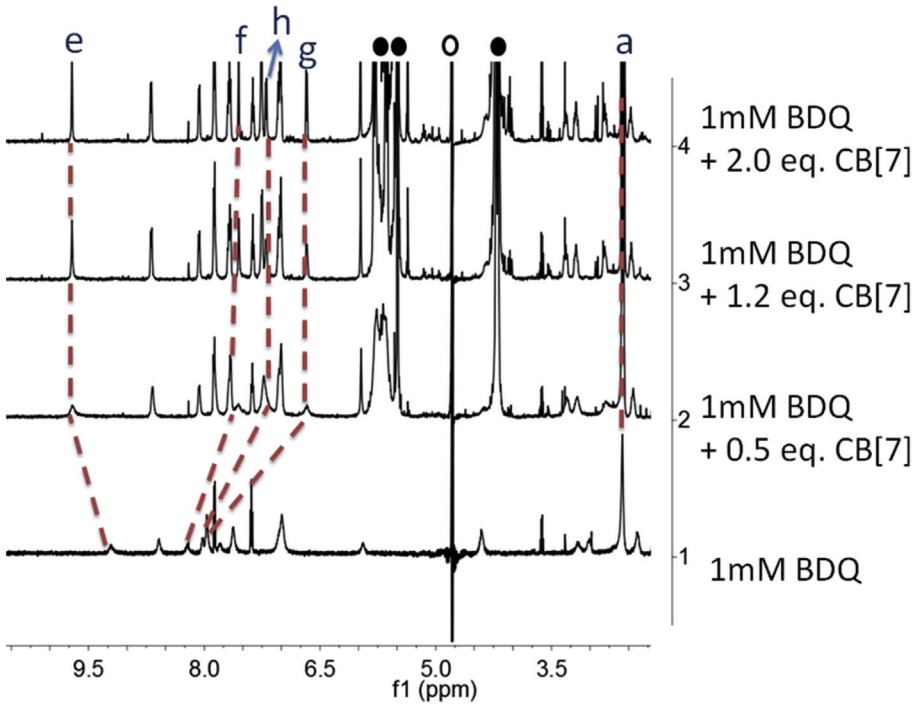

Fig. 2. The stacked ^{1}H NMR spectra of BDQ (1 mM) in the absence and in the presence of CB[7] (0.5 and 1.2 and 2.0 equivalents) at pD = 2. The peaks corresponding to CB[7] are labeled as (●) and the HOD peaks as (○). Dotted lines indicated that the protons on BDQ experienced upfield or downfield shifts with increasing amounts of CB[7].

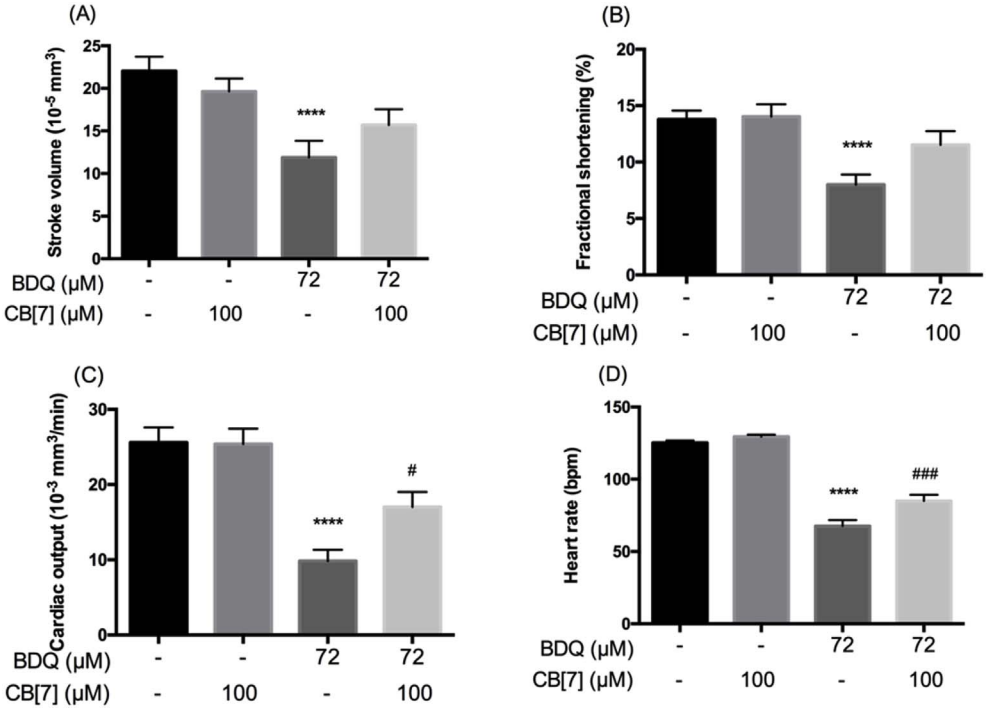

Fig. 4. Cardiac functions of zebrafish (2 dpf) exposed to CB[7] (100 μM), BDQ (72 μM), and CB [7]-BDQ (100 μM:72 μM) for 2 days. Stroke volume (A), fractional shortening (B) cardiac output (C) and heart rate (D) of zebrafish hearts are shown. Data are plotted as mean ± S.E.M (n = 10–15). All experiments were conducted for three times. $^{****}P < .0001$, for comparison with control group; $^{\#}P < .05$, $^{\#\#\#}P < .001$, for comparison with BDQ treated group.

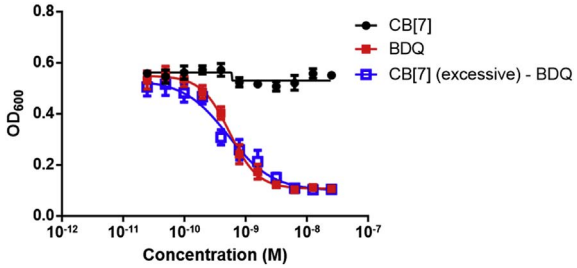

Fig. 5. Effects of BDQ, CB[7], and CB[7]-BDQ against the growth of *M. smegmatis*. The MIC_{50} is (5.51 ± 1.16) x 10^{-10} M and (5.59 ± 2.3) x 10^{-10} M for BDQ and CB[7]-BDQ (excessive CB[7]) complex respectively.

2.3. HPLC phase solubility analysis

HPLC phase solubility experiments were conducted with Agilent 1200 series HPLC (Agilent Technologies, Santa Clara, California), and the integration of the peaks was processed with the built-in software. Phase solubility analysis was carried out following the procedures reported (Shengke Li et al., 2016), Briefly, a standard curve of BDQ was established with a HPLC-UV method. Afterwards, a 2 mM stock solution of CB[7] in acetonitrile was prepared. Various concentrations of CB[7] (2.0, 1.6, 1.0, 0.8, 0.5, and 0.2 mM) that was diluted from the stock solution were used to dissolve excess amounts of BDQ. The solutions were subject to sonication and shaken overnight. On the next day, solutions were centrifuged (13 200 rpm, 10 min), 0.3 mL supernatant aliquot from each solution was added to 1-adamantylamine (6 mM, 0.2 mL). Each mixture was subsequently vortexed and sonicated. Precipitated BDQ was dissolved in CH_3CN (0.3 mL) in each vial and the resulting solution was filtered for HPLC experiment. BDQ was separated following a literature method (Cuyckens et al., 2008), and the chromatographic column used was a ZORBAX Eclipse XDB-C18 column (150 × 4.6 mm, 5 μm; Agilent Technologies). During the separation, gradient elution method with two solvents (denoted as A and B) was used. Solvent A consisted of 0.1 M ammonium acetate solution (pH 7.5) and solvent B was mixture of 10% of 1 M ammonium acetate solution (pH 7.5), 45% methanol, and 45% acetonitrile. The column and autosampler were maintained at room temperature during the experiments.

2.4. Zebrafish maintenance and husbandry

Zebrafish (*Danio rerio*) were raised in the zebrafish housing system at the Institute of Chinese Medical Sciences, University of Macau and maintained as described in the Zebrafish Handbook. A cardiac-specific fluorescent transgenic zebrafish line Tg(*cmlc2*:GFP) with green fluorescent protein (GFP) expressed in myocardial cells were adopted for cardiotoxicity evaluation. Fertilized zebrafish embryos were collected after natural spawning and merely the healthy embryos were selected for subsequent experiments. Embryos were cultured at 28.5 °C in E3 medium (5 mM NaCl, 0.17 mM KCl, 0.33 mM $CaCl_2$, and 0.33 mM $MgSO_4$ at pH 7.2–7.3). All experiments were conducted according to the ethical guidelines and animal research ethics protocols approved by the Institute of Chinese Medical Sciences Animal Ethics Committee, University of Macau.

2.5. Cardiotoxicity evaluation

Tg(*cmlc2*:GFP) zebrafish larvae were used for cardiovascular function studies. Zebrafish embryos were kept in E3 medium containing 0.003% (wt%) of 1-phenyl-2-thiourea (PTU) to prevent pigmentation since 1 dpf (days post fertilization). The healthy 2 dpf zebrafish larvae were employed and randomly placed into the 12-well microplate with 10–15 larvae per well for treating with 1 mL of BDQ (72 μM) in the presence or absence of CB[7] (100 μM). After 2-day incubation, zebrafish embryos were embedded into 1% (wt%) of low melting point agarose for orientation and position fixation and movement restriction. 15-second video of beating hearts from individual larvae at the end of incubation was recorded to obtain the heart morphology and for quantitative assessment of ventricular function by using an Olympus Cell^R imaging system comprising a IX71 microscope at room temperature. Ventricular function was evaluated with heart rate (HR), stroke volume (SV), cardiac output (CO), and fractional shortening (FS). The HR was determined by counting the number of heartbeats in a 15-second interval. Images from the video were used to measure the longitudinal axis length (a) and lateral axis length (b) between the myocardial borders of ventricles at end-diastole and end-systole, respectively. The ventricular volume at end-diastole (EDV) and end-

systole (ESV) in the larvae was calculated from the heart dimensions using the formula for a prolate spheroid: $V = 4/3\pi ab^2$. The SV, CO and %FS were calculated as follows: SV = (EDV − ESV), CO = SV × HR, % FS = (Diastolic diameter − Systolic diameter)/(Systolic diameter) × 100%. The average value of each parameter gained from three independent biological replicates was extrapolated to assess the cardiac functions of the zebrafish larvae.

2.6. Bacterial strains and growth condition

Mycobacterium smegmatis (*MS*) MC2155 was used for the bacterial inhibitory assay to determine the minimum inhibitory concentration (MIC). *MS* was cultured in Middlebrook 7H9 broth supplied with 0.2% glycerol, 0.05% Tween 80, and 10% ADS (albumin–dextrose–saline) at 37 °C.

2.7. Minimum inhibitory concentration determination

Minimum inhibitory concentration (MIC) of BDQ and CB[7]-BDQ complex towards *MS* was examined in 7H9 medium as described previously (Kurabachew et al., 2008). Briefly, BDQ dissolved in DMSO, CB [7] and CB[7]-BDQ dissolved in medium were 2-fold serially-diluted and seeded in 96-well plates, resulting in 10 dilutions for each of the compounds/mixtures. A volume of 200 μL of *MS* MC2155 culture at final OD_{600} = 0.02 was added to each well containing the testing compounds. The plates were subsequently incubated at 37 °C for 48 h and the growth of bacteria (OD_{600} value) was recorded using a Tecan Infinite M200 PRO Multifunctional Microplate Reader. The MIC_{50} curves were plotted using GraphPad Prism software.

2.8. Statistical analysis

All data were presented as mean ± standard error derived from three independent replicates. Diagrams and statistical analysis using a one-way ANOVA was calculated by GraphPad Prism Software (GraphPad Software, La Jolla CA, USA). P-values of less than 0.05 were considered statistically significant.

3. Results and discussion

3.1. ^1H NMR study

NMR has been widely used to investigate the binding site and binding geometry within a host-guest complex, particularly CB[*n*] based host-guest complexes. The protons on the guest compound would experience shielding effect if they are encapsulated inside the cavity of CB[*n*] therefore exhibiting upfield resonance shifts. If it is located just outside the cavity but near the portal of the CB[*n*], these guest protons would be deshielded and exhibit downfield shifts (Wang et al., 2009). Therefore, NMR was employed to investigate the binding sites and geometry of the CB[7]-BDQ host-guest complex. With the aid of COSY NMR, the chemical resonances corresponding to the protons of BDQ were assigned (Supporting information Fig. SI.1). Fig. 2 shows the ^1H NMR spectra of BDQ in the absence and in the presence of 0.5, 1.2 and 2.0 equivalents of CB[7]. This stacked spectra showed that H^f, H^g and H^h of BDQ experienced upfield shifts with increasing amounts of CB[7], suggesting that these protons were encapsulated inside the cavity of CB [7]. On the other hand, H^e is the only proton that showed an obvious downfield shift, suggesting that it was sitting outside the cavity but by the carbonyl portal of CB[7]. Meanwhile, other aromatic protons (phenyl and naphthyl) as well as aliphatic protons (such as H^a) didn't exhibit observable shifts, suggesting that these moieties were not complexed by CB[7]. Collectively the ^1H NMR results suggested that CB [7] likely encapsulated the bromobenzyl moiety of BDQ to form 1:1 host-guest complexes.

3.2. HPLC phase solubility

Several reports have demonstrated that CB[7] may improve the solubility of poorly soluble guest drugs as analyzed by a phase solubility method (Liu et al., 2015). In addition, phase solubility diagram also offers complexation information such as binding stoichiometry and binding constant of a host-guest complex (Zhang et al., 2011). As shown in Fig. 3, the solubility diagram of BDQ and CB[7] as analyzed by HPLC method, the aqueous solubility of BDQ increased linearly along with the increasing amount of CB[7], suggesting a 1: 1 binding stoichiometry between the CB[7] and BDQ (Higuchi and Connors, 1965). On the other hand, the slope of the linear fitting curve implied that the solubility of BDQ was increased upon complexation, reaching a concentration of up to approximately 0.27-fold of the maximum solubility of CB[7]. By using the intrinsic solubility (S_o) of BDQ and the slope of the phase solubility diagram, the binding constant (K_a) can be calculated as followed K_a = [slope/S_0 (1- slope)]. The intrinsic solubility of the BDQ is defined to be "very slightly soluble (VSS) in 1M HCl" by the EMA and according to United State Pharmacopeia 30/NF25, VSS compound has a solubility ranging from 1 to 0.1 mg/mL. Our phase solubility curve suggested the S_0 at neutral pH conditions was approximately 0.093 mM and K_a is calculated to be $3.98 \times 10^3\ M^{-1}$. By forming CB[7]-BDQ supramolecular host-guest complex. CB[7] could potentially be used to formulate BDQ.

3.3. Effect of CB[7] on the cardiotoxicity of BDQ in vivo

Tg(*cmlc2*:GFP), a transgenic zebrafish with GFP expressed in myocardial cells, was employed for the evaluation of the effects of supramolecular complexation of BDQ by CB[7] on its inherent cardiotoxicity. Zebrafish larvae were treated with BDQ in the absence or the presence of CB[7]. Cardiac functions were monitored by a set of physiological parameters including stroke volume (SV), fractional shortening (%FS), cardiac output (CO) and heart rate (HR) from the videos and images of the zebrafish embryo hearts. As shown in supporting information Fig. SI.2 the fluorescent images and Fig. 4 the cardiac functions including SV, %FS, CO and HR of zebrafish treated with 100 μM of CB[7] were comparable to those of the blank control group, attesting its good biocompatibility and the observations are consistent with our previous studies (Chen et al., 2015; Li et al., 2015). Conversely, BDQ (72 μM) induced cardiac dysfunctions exhibiting dramatically reduced SV, %FS, CO and HR, in comparison with the control group. When incubated with BDQ (72 μM) in the presence of CB[7] (100 μM), the improvement of, CO and HR of zebrafish hearts were obvious, although being moderate, when compared to those treated with BDQ alone, suggesting that CB[7] is able to alleviate the inherent cardiotoxic effects of BDQ in this zebrafish model. The reduced cardiotoxicity is likely due to host-guest interactions between the drug and the host that limits the drug's cardiac uptake or interactions with its toxicological receptor, and the moderate degree of improvement is probably attributed to the ineffective host-guest interactions at this concentration range (~100 μM).

3.4. Antimycobacterial effect of CB[7]-BDQ complex

TB is caused by *Mycobacterium tuberculosis* (*Mtb*) infection and BDQ is an approved anti-TB drug that has very promising antimycobacterial effect. Thus, the therapeutic effect of BDQ in the absence and in the presence of CB[7] was assessed using *Mycobacterium smegmatis (MS)*, a non-pathogenic mycobacterial strain that biologically resembles *Mtb*. Fig. 5 shows that the anti-*MS* properties of BDQ was not significantly affected with the presence of CB[7], with MIC_{50} of $(5.51 \pm 1.16) \times 10^{-10}$ M and $(5.59 \pm 2.3) \times 10^{-10}$ M) for BDQ and CB[7]-BDQ (excessive CB[7]), respectively. Overall, antimycobacterial assay confirmed that the efficacy of BDQ was well preserved when formulated with excess amount (100 μM) of CB[7].

4. Conclusion

In this study, BDQ, a very slightly soluble anti-TB drug, formed 1:1 binding complex with the macrocyclic receptor CB[7] yielding a binding constant in the order of magnitude of approximately 10^3 M^{-1} determined by HPLC-UV phase solubility analysis. Upon CB[7]-BDQ complex formation, the solubility of BDQ was increased up to approximately 0.27-fold of the maximum solubility of CB[7]. More importantly, the complexation of CB[7] significantly reduced the cardiac malfunctions caused by BDQ in *in vivo* zebrafish model. On the other hand, *in vitro* antimycobacterial MIC assay suggested that the antimycobacterial efficacy of BDQ towards *Mycobacterium smegmatis* was almost not affected upon its complexation with CB[7], indicating that CB[7] improved the aqueous solubility, alleviated the inherent cardiotoxicity, and maintained the antimycobacterial efficacy of BDQ at the same time. This report provides additional evidence to support the potential use of CB[7] in formulating therapeutic molecules such as anti-TB drugs, for improving the physiochemical properties, reducing side-effects as well as potentially enhancing therapeutic efficacies of included drug molecules.

Acknowledgement

We acknowledge Research Committee of University of Macau (Grant No.: MYRG2016-00008-ICMS-QRCM) for providing financial support to this research.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.12.022.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.12.022.

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