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Mechanisms for Improving the Clinical Success of a Low-Water Soluble New Drug Moiety, the Bedaquiline Case Study

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Abstract

Multidrug-resistant tuberculosis (TB) is a disease commonly found in people living with HIV in many low-income economies of the world, with South-East Asia [44%] and Africa [25%] accounting for the highest percentage of infections. The nature of the cell wall of the bacteria causing this disease makes it difficult for drug molecules to penetrate the envelope in sufficient concentration to kill the organism. Bedaquiline has been found to have bactericidal action when used together with other drugs in the treatment regimen for TB. Bedaquiline is a highly lipophilic drug (clog P 7.25) and the fumarate salt is currently the only available commercial drug product. New salts of bedaquiline have been formed and are being investigated as potential alternatives to increase the availability of commercial products.

The current effort reviewed the structural activity relationship of bedaquiline, and its pharmacodynamic and pharmacologic profiles, to delineate the mechanisms underlining its bactericidal activity on mycobacterium tuberculosis. The review also covered some preclinical formulation that has been used in bedaquiline as possible strategies to be used in developing the new salts.

Keywords: Benzoate; Maleate; Tuberculosis; Cell membrane; Solubility strategy

Background

Tuberculosis (TB) is a communicable disease that the World Health Organization (WHO) ranks as one of the top ten causes of death from a single infectious agent. The cell wall of the causative agent, bacillus Mycobacterium tuberculosis, consists of about 50% of mycolic acid which is very hydrophobic and limits the ingress of drug molecules [1]. The bacterium typically affects the lungs (pulmonary TB), or other sites (extrapulmonary TB); incidence is higher in men than women [2]. However, the COVID-19 pandemic adversely impacted the reporting rate of TB globally, a decline of 7.1 million in 2019 to 5.8 million in 2020 [3]. The disease can be treated with a six-month regimen, though the current treatment coverage access reported by WHO in 2020 still fell short of the universal health coverage (UHC) milestone [4]. The UHC 2025 milestone for reducing TB deaths is that if everyone with the disease can receive their treatment without financial hardship, the mortality rate can be reduced to 6.5% [3]. The WHO regions of South-East Asia [44%] and Africa [25%], account for a higher percentage of people living with the disease [2]. Furthermore, recent findings indicate a higher number of deaths from TB infections among people living with HIV also occurred in these regions [3]. Bedaquiline is used as a combination therapy to treat to treat multi-drug resistant tuberculosis (TB) in adults [≥ 18yeras] and was approved by the US FDA on December 28, 2012. Fumarate salt is the commercially available option. However, to provide alternative compounds as new molecular entities and improve accessibility to the product, a Purdue University salt project screened and synthesized new benzoate and maleate salts of bedaquiline to 10g scales [5]. Under the FDA label, bedaquiline was described as a water-insoluble compound. The purpose of this review is to explore possible mechanisms that were employed to develop a clinically acceptable product such as Sirturo. The product is marketed by Janssen Cilag as 100mg tablets of the fumarate salt of bedaquiline. We will then suggest similar concepts to formulate the newly synthesized salts of bedaquiline.

Factors that Impact Drug Bioavailability

After the discovery of a new drug based on a pharmacological effect or drugability, several steps are required to improve its chances of clinical success. These optimization processes often involve modifications of the lead candidate to generate compounds that can be formulated to meet the desired product performance in clinical trials. Some factors that govern drug performance include the physicochemical properties of the final API, the physicochemical properties, and the formulation of a drug product. Another factor is the physiological components within the body that impact the responses to the presence of a drug compound [6].

The physiological factors that can influence drug absorption include the absorptive surface area, pH fluctuations in the GIT, permeability, dietary effects, protein binding, and clearance mechanisms. While the physicochemical properties include the drug's solubility, physical and chemical stability, molecular size and shape, pKa of the ionizable part, and the physical state (amorphous vs crystalline, solvates vs hydrates, liquid vs gaseous, and polymorphs) [6]. The solubility of a drug impacts its rate of dissolution and absorption, and ultimately its bioavailability. The reported aqueous solubility for bedaquiline is 0.000193 mg/mL [7].

Drug absorption may also be influenced by the use of some excipients that can modulate some physiological properties of a system. Cyclodextrins, surfactants, and cosolvents have been shown to modulate membrane transporters and impact drug absorption [8]. In assessing the impact of amorphous solid dispersion, PVP increased the bioavailability of nifedipine [6]. It was reported that acacia (suspending agent) interferes with pain and inflammation, and should be avoided in studies related to those symptoms. Also, PEG 400 should be avoided in studies for insulin release (e.g. OGTT), while Cremophor EL (emulsifier) has a strong affinity for plasma proteins. These examples re-iterate the importance of knowledge-based decisions in choosing vehicles for drug formulations [9].

What happens to an orally administered drug product

Oral bioavailability has mostly been described in terms of absorption (A), distribution (D), metabolism (M), and excretion (E) or ADME of the drug. Aside from permeability across epithelial cells, from the traditional approach, orally administered drugs are expected to de-aggregate and dissolve; the freely soluble drug may then undergo either of the following: endocytosed by intestinal flora, taken up into bile micelles, nucleate into other solid-state forms, interact with endogenous or exogenous compounds found within GI milieu [10].

The freely soluble drug may also undergo chemical or enzymatic degradation, as well as interact with other potential cofounders such as food, pH, protein binding, etc. All of these factors may decrease the amount of the drug that can be absorbed. The existence of an unstirred water layer that lies on top of the mucus and then the glycoprotein and sialic acid-rich glycocalyx forms an unstirred aqueous boundary layer (ABL). The rate-limiting step for lipophilic drugs is determined by this ABL [11]. To demonstrate some of the complexities involved in drug absorption, Darwich et al simulated the process using an "Advanced Dissolution, Absorption, Metabolism (ADAM)" model, [Symcyp®]. Their model demonstrated the various regions of the

intestine (duodenum; the upper and jejunal regions; the upper, middle, and middle-lower, and terminal ileum; and the colon), the varying transporter and enzyme expression along the GI tract, the ABL and luminal contents. Their model demonstrated that regional absorption can differ dramatically based on the drug [12].

Based on in vivo and in vitro evidence from marketed drugs, drugs are transported across cell membranes by passive transcellular and carrier-mediated processes. Earlier studies had suggested that the passive transcellular process was the predominant mechanism, however more recent studies have described carrier protein transporters for many drug molecules [13-15]. Both mechanisms are known to coexist, and the predominant process is determined by the drug and the membrane. Carrier-mediated transport involves membrane proteins in the transcellular permeation. There are more than 400 membrane proteins, subclassified under 2 major families, the ATP-binding cassette (ABC) and the solute carrier (SLC). When energy (ATP) is required for the permeation process, it's described as active transport, which may not require a concentration gradient. However, if the carrier mechanism does not require energy, it is termed a facilitated transport, which is saturable (except where glucose or amino acids are the transporters) and depends on a concentration-dependent on a substrate, as well as a transporter protein [16,17].

Method of Review

Objective

The review aimed to aid the understanding of the properties of the bedaquiline system, and proffer strategies that may be used for improving the aqueous solubility of the new salts of bedaquiline.

Methodology

As demonstrated in Figure 1, we reviewed literature that provided information on the structure of the bacteria that causes tuberculosis and why it is resistant to several medications. Also, publications provided the background on the structure-activity relationship and other physicochemical properties of bedaquiline, as well as its mechanism of action. Finally proposed formulations that have been used to enhance the solubility of lipophilic drugs, as strategies to improve the bioavailability of the new salts of bedaquiline.

Results and Discussions

Bedaquiline case study

Bedaquiline belongs to BCS class II, having low solubility, and high permeability. The leaflet of the commercially available fumarate salt, Sirturo[R], provided the formulation properties. The excipients list: colloidal silicon dioxide, corn starch, croscarmellose sodium, hypromellose 2910 15 mPa.s, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and polysorbate 20. The product is supplied as uncoated tablets packed in HDPE bottles and should be taken with meals. After the drug is administered it has to cross several physiological barriers before it can enter the systemic circulation and exert its bactericidal function at the target sites. Some physicochemical properties of bedaquiline are listed in Table 1.

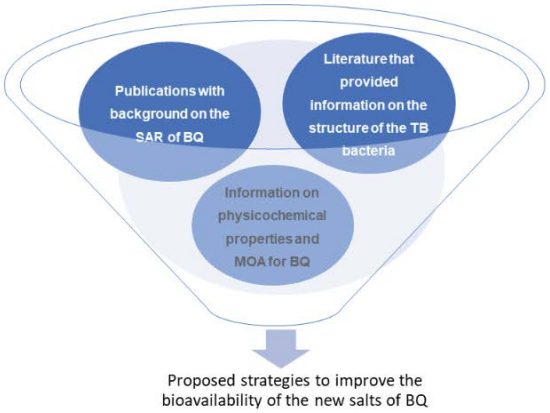

Figure 1: Methodology for review.

Some guidelines have been proposed as predictors for ADMET profiles of compounds in drug discovery. Lipinski rule of 5, Ro5 (compounds which have one or more of either cLogP > 5, MW > 500, # of H-bond acceptors > 10 or # of H-bond donors > 5, are less likely to be orally absorbed), has been adopted as a good predictor of drugs with good oral absorption [18]. Research from Astra Zeneca suggested that Lipophilic Ligand Efficiency (LLE, pIC50 – cLogP), when > 5, predicts a compound with lower relative toxicity [19]. Similar research from Pfizer (3/75 rule) predicts six-fold lower toxicity for compounds with cLogP < 3 & Total Polar Surface Area TPSA >75. The GSK 4/400 rule predicts a CLogP < 4 and an MW < 400 indicates a favorable ADMET profile [20]. Another study suggested that a compound with < 3 aromatic rings will favor oral candidacy. GSK, further modified the aromatic rings prediction, to include Property Forecast Index PFI (sum of a chromatographically measured logD at pH 7.4), if < 6, predicts a more soluble drug with better ADMET [19]. Polanski et al described Lipinski's rule and the other reductionist views, as the drug-likeness approach. The group postulated that the average molecular weight and cLogP of the average marketed drug are 300-450 Da, and 1.5-4.0, respectively [21]. In line with these postulates, and based on the physicochemical properties of bedaquiline listed in Table 1, the molecule is expected to be highly water insoluble, which would be a challenge for bioavailability.

Why is it difficult to treat TB?

Mycobacterium tuberculosis genome sequence identified multiple targets for potential therapeutic intervention, however, TB discovery programs that identified potent invitro inhibitors of mycobacterium tuberculosis largely fail to translate to success in vivo. This is largely due to the inability of the drug moieties to permeate the TB bacterial cell wall (envelope) [22], see Figure 2 [23].

Table 1: some properties of the bedaquiline system.

Property	Value
molecular weight	555.505 Daltons
chemical formula	$C_{32}H_{31}BrN_2O_2$
water solubility	0.000193 mg/mL
logP	6.37
polar surface area	45.59 Å^2
number of rings	5
acceptor count	4
hydrogen donor count	1

Source: (DRUGBANK, 2021) [7].

Figure 2: CDC.gov illustration of the cell membrane for mycobacterium tuberculosis (CDC.gov, 2021).

The intrinsic drug resistance observed in the TB bacteria has been linked to the following factors

The structure of the bacterium cell wall: The cell envelope has been described as having three coatings, namely: an outermost capsule made up of proteins, glucans, and lipids. The second layer is a cell wall made of mycomembrane (MM), arabinogalactan (AG), and inner peptidoglycan (PG), there is also a cell membrane [24]. The mycomembrane is made up of phospholipids and long-chain mycolic acids which makes it difficult for drug molecules to penetrate the cell wall of the bacterium [25]. This barrier makes it difficult for drugs like rifampicin and fluoroquinolone antibiotics to penetrate in sufficient amounts to be bactericidal against the organism [26,27]. Another study investigated targeting the dTDP-4-dehydrorahmnose reductase (RmlD) which is the final enzyme in the series of cell-wall proteins of the TB bacteria. The study further proposed use of drugs that block hydrogen bonding linked to ligand-567 as a potential inhibitor of the RmID enzyme would be successful in treating the disease [28].

Efflux pump proteins: An active efflux mechanism that regulates the concentration of drug molecules expels chemical compounds and toxins entering the bacterial and human cells. This regulatory mechanism has been reported to be responsible for mycobacterium resistance to drugs like tetracyclines and aminoglycosides [29].

Enzymatic degradation and modification of drug molecules: Several enzymes produced by the mycobacterium that causes TB has been shown to either modulate or modify the actions of many anti-infective agents such as macrolides and aminoglycosides [30,26]. Ordinarily, beta-lactams disrupt the formation of the bacteria cell wall by binding to their transpeptidase to inhibit crosslinking required for their cell wall synthesis. However, the mycobacterium tuberculosis produces beta-lactamase enzyme which makes degrades the beta-lactam rings in drugs like carbapenem and meropenem [30]. Furthermore, chemical modifications such as methylation and acetylation of some aminoglycosides such as kanamycin have rendered them ineffective against the TB bacteria [27].

Drug resistance from prolonged treatment schedule: The long treatment regimen for TB is another reason for the difficulties encountered in handling patients. Poor adherence to the treatment regimen has been implicated as a risk factor for developing resistance to TB medications. Reports from clinical trials using patients with latent and active TB indicated that poor treatment outcomes were linked to the disease course regimen [31,32]. Some population of the mycobacterium has been reported to tolerate the antibiotic regimen over the prolonged course of treatment and can cause reinfection after the TB drugs are withdrawn [25,30]. However, the average global resistance to treatment with fluoroquinolones remains at about 50% in the WHO regions outside Europe [3].

Chemical structure of bedaquiline

Bedaquiline [1-(6-Bromo-2-methoxy-quinoline-3-yl)-4-dimethylamino-2-naphthalen-1-yl-1-phenyl-butan-2-ol] with a molecular formula of $C_{32}H_{31}BrN_2O_2$ has a molecular weight of 555.51 Daltons. It contains planar hydrophobic moieties (hydroxyl and N, N-dimethyl(-$N(CH_3)_2$) groups (which bind to mycobacterium F1/F0-ATP synthase), and hydrogen-bonding acceptor or donor group. The dimethyl group also binds to amino acid residues Arg-186 and Glu-61 at the A and C subunits; the H-bonding provides structural stability. The diarylquinoline ring, the hydroxy group, and the naphthalene moiety, all play important roles in the anti-TB activity of bedaquiline. It acts synergistically with first and second-line drugs for the treatment of TB [33].

Bedaquiline is a cationic amphiphilic drug (CAD) because it has a hydrophobic ring structure as well as a hydrophilic side chain (OH-group) with a cationic amine group (NMe_2) that can become protonated at physiologic pH values [34].

Structure-Activity-Relationship for pyridyl group of bedaquiline

After the discovery of a lead compound, further investigations are carried out to improve the developability of the moiety to improve its success in clinical trials. This can often be accomplished by modifications of side chains or units of the lead candidate. Bedaquiline has a long half-life, low water solubility [0.000193 mg/mL], and high lipophilicity (clogP 7.25). It can form salts at the nitrogen group with the more basic pKa 8.91 [35]. Some studies investigated analogs that will possess similar or improved antimicrobial potency, but with lower lipophilicity than bedaquiline. They reported lower lipophilicity (clogP) by replacing the lipophilic 6-Br group on the quinoline ring (A-unit), with a more hydrophilic cyano group [36,37], see Figure 3. Similarly, substituting the phenyl group (B-unit) with a monoheterocyclic group of widely differing lipophilicity (thiophenes, furans, pyridines), also published lower lipophilicities and improved MIC_{90} [38]. Replacing the very lipophilic naphthalene (C-unit) with some less lipophilic bicyclic heterocycles yielded average lower clogP limits of about 5.0. Some of the compounds also showed less QT prolongation effect from a significant reduction in inhibition of hERG channel potassium [39].

PK/PD properties of bedaquiline

The drug has a T_{max} of 5hrs after an oral dose; food increases the oral bioavailability. Administering 400 mg of bedaquiline once daily

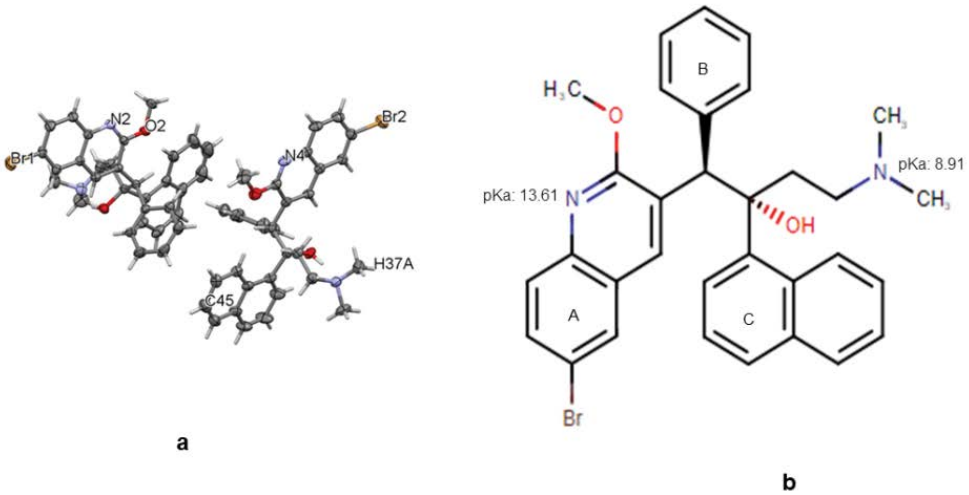

Figure 3: a) single crystal structure of bedaquiline. b) the subunits of the bedaquiline system were manipulated for possible improved activity.

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for a week, gave a peak plasma concentration (C_{max}) of 5.5 μg/mL and AUC of 64.75 μgh/mL. The volume of distribution was reported to be 164L, this low value indicated that it is >99.9% bound to plasma proteins. Through the hepatic system, the drug is mainly metabolized by CYP3A4 to N-monodesmethyl metabolite (M2). This metabolite is 4-6 times less active than the parent compound in terms of antimicrobial potency. Bedaquiline is primarily eliminated through the fecal route, while renal clearance of the unchanged drug is insignificant. The effective half-life is 24–30 hours [40], and the terminal half-life of bedaquiline and M2 is 5.5 months, which suggests that M2 bind to peripheral tissues, and is slowly released [7].

Bedaquiline is a diarylquinoline compound with a bactericidal action against Mycobacterium tuberculosis. The reported mechanism of action is through the inhibition of the proton pump of mycobacterial ATP (adenosine 5'-triphosphate) synthase. The pharmacodynamic property of bedaquiline is primarily oxidative metabolism leading to the formation of M2, which is not thought to contribute significantly to clinical efficacy but appeared to correlate with QT prolongation. Bedaquiline has a minimal inhibitory concentration (MIC) from 0.002-0.06 μg/mL and an MIC_{50} of 0.03 μg/mL, against the tuberculin bacteria. Also, dormant nonreplicating bacilli bacteria with smaller ATP stores are more susceptible to bedaquiline [7].

PK/PD modeling of bedaquiline that predicts shorter treatment regimen for multidrug-resistant TB: The current WHO regimen for directly observed (DOT) treatment of multi-drug resistant TB (MDR-TB) is a six-month course with a modest global treatment success rate of 52% [4]. The currently recommended 6-month regimen for people with drug-susceptible TB disease is with four first-line drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide. Patients that have been identified as being resistant to isoniazid can be treated with rifampicin, plus any fluoroquinolone, plus at least one of the drugs bedaquiline and linezolid. There is also a proposal for a 6-month regimen (bedaquiline, pretomanid, and linezolid), and many countries have included bedaquiline in the regimen for treating drug-resistant TB patients [3].

Based on assumptions from other studies that optimized treatment for malaria [41], a mathematical model and in-silico modeling was used to predict if bedaquiline containing regimen could provide shorter treatment periods for MDR-TB. The model combined the intra-host dynamics of M. tuberculosis in a human host environment, with PK-PD models of anti-TB drugs to simulate possible short-course regimens treatment for MDR-TB with bedaquiline. The simulation suggested that bedaquiline when administered daily for two weeks during the intensive therapy phase, could reduce the treatment period to a 4-month regimen [42].

Undesirable effects of bedaquiline: Bedaquiline caused inhibition of the hERG (human Ether-à-go-related gene; KCNH2) potassium channel (concurrent risk of cardiac toxicity, delayed ventricular repolarization) [43]. In rat studies, both the M2 metabolite and the parent drug-induced phospholipidosis. The amphiphilic nature of bedaquiline and M2 enables them to penetrate the membranes of lysosomes. The acid environment in the lysosome protonates the amine group which can block further diffusion, and traps the protonated drug molecule inside the lysosome. The trapped drug inhibits phospholipases, this inhibition of phospholipid degradation can lead to phospholipidosis [34]. The highly lipophilic nature (clog P 7.25) contributes to its long terminal half-life (5.5 months), and in general greater tendency for liver toxicity [43].

Certain drugs have been identified as inducers of P450 enzymes. When such drugs are co-administered with others that are metabolized by this enzyme, it renders them less effective, requiring higher doses for efficacy. CYP3A4 has been identified as the hepatic enzyme that metabolizes bedaquiline. TB regimen involves the use of multiple drugs; therefore, co-administration of inducers or inhibitors of CYP3A4 will impact bedaquiline concentration. Rifampicin induces CYP3A4 and decreased the AUC of bedaquiline by 52% in a 21 day study of healthy volunteers. Also, CYP3A4 inhibitors like ketoconazole increased levels of bedaquiline [7,34]. Co-administration with CYP3A4 inducers/inhibitors should be monitored or avoided.

Possible mechanisms of antimycobacterial action of bedaquiline

The drug selectively targets and inactivates the F1/F0-ATP synthase of MDR strains mycobacteria, without inhibiting the mammalian F1/F0-ATP synthase. Bedaquiline generally exhibits MIC values greater than 32 mg/L [44]. In-silico molecular modeling/docking has identified the lipophilic F0 component of F1/F0-ATP synthase, specifically the trans-membrane oligomeric subunit C (AtpE), as the primary target of bedaquiline [45]. Bedaquiline is a cationic amphiphilic moiety, which suggests an alternative mechanism for its antimycobacterial action; possibly related to its effects on membrane ion-transporting ATPases [33]. It is also postulated that mycobacterium tuberculosis may allow direct diffusion of hydrophobic molecules across its lipid membranes or via porins and/or carrier proteins. The evidence for this passive diffusion through a 'hydrophobic pathway' stems from the fact that many TB drugs are lipophilic, also, membrane modulations through changes in temperature or mycolic acid content could lead to increased uptake [22]. To gain access to the cytoplasm of TB mycobacterium, drugs must cross the waxy outer mycomembrane and then cross the inner membrane [46]. Porins from channels in the outer mycomembrane, and are important in controlling the influx of nutrients, glycerol, haem, and antibiotics [47]. The mycobacterium membrane is postulated to contain at least 37 ATP-binding cassettes (ABC) transporters and 30 major facilitator permeases [48].

Efflux pump inhibition improved potency of bedaquiline

Microbial resistance to TB agents is thought to be partly mediated by an efflux mechanism from cell membranes. When ingested by the host phagocytic cells, TB mycobacteria remains viable even in the presence of several antibiotic agents. Mycobacteria tuberculosis uses efflux pumps to remove xenobiotics, including drugs that would have otherwise killed it [49]. About 30 different efflux pumps from five major superfamilies have been linked to drug resistance in *Mycobacterium tuberculosis* [50]. It was shown that the mammalian efflux pump inhibitor timcodar (at 10g/mL combined with a diverse set of anti-TB antibiotics) potentiated the activity of bedaquiline in broth culture against mycobacterium tuberculosis. Timcodar conferred a 15-fold improvement in the MIC (MIC 0.004g/mL with timcodar versus 0.06g/mL without timcodar). The study found that combinations of timcodar with rifampicin, bedaquiline, and clofazimine showed synergy in broth cultures [49]. However, more recent studies provided evidence that suggests that the bacterial efflux pumps enable the development of resistance against drugs such as bedaquiline and clofazimine [51]. Although plant-based efflux pump inhibitors have been identified as potential viable anti-TB agents [52], there are a plethora of challenges associated with developing such naturally occurring alkaloids, phenolic compounds (flavonoids, polyphenols), and terpenes as drug molecules [53].

In-vitro and animal models used for bedaquiline studies

Whole-cell assays were used to concurrently assess multiple targets for bedaquiline. The study evaluated the drug's activity against *M. tuberculosis* in log-phase growth at levels of 10 and 100 times the MIC. The results obtained results suggested bactericidal time-dependent activity of bedaquiline [40]. However, further evaluation with a murine model, showed that the AUC in vivo results from bedaquiline studies more closely resembles concentration-dependent killing [54]. Due to similarities between human and bovine TB infections, guinea pig models were used in several studies [55,56].

In TB pathogenesis, cavities can form from the liquefaction of cesium and are considered central to its spread and persistence. A study evaluated bedaquiline's ability to penetrate caseous centers, using a predictive *in vitro* assay that measures drug binding to *ex vivo* caseum. The rapid equilibrium dialysis (RED) device consists of 2 chambers separated by a semi-permeable membrane with an 8 kDa molecular weight cut-off. There was a correlation between fraction unbound (f_u) and diffusion into caseum *in vivo* for bedaquiline [57].

Potential strategies for bedaquiline formulations

Formulations can influence the release, absorption, metabolism, and bioavailability of a drug. Pharmaceutical scientists have used developed different formulations that have altered the bioavailability of erstwhile low solubility drugs, to achieve levels at which they can meet their desired PK PD response. In pre-clinical settings, formulations can be delivered as solutions, suspensions, and amorphous dispersions of solid drugs. When the solid-state properties of an API are well characterized, suspensions are commonly used as surrogates to predict exposure levels from tablets or capsules. Common compositions of such suspensions are API mixed with 1-10% cellulose polymer and 0.1-0.2%w/v surfactant [9]. In contrast to the use of micronized drug particles where particles are in the 2–5 µm range, the use of submicron nanoparticles (less than 1µm range) with larger surface area, improves dissolution rates. Nanoparticles colloidal suspensions usually incorporate appropriate wetting agents and coating polymers that prevent aggregation of the nana-sized drug particles [9].

Other strategies used for pre-clinical formulations include pH adjustments, where drug molecules are formulated to promote their solubilities in the biorelevant liquids based on their ionization potentials [9,58]. Also, amphiphilic compounds such as surfactants, which can form micelles that help improve the apparent solubility of lipophilic drugs, have been used to improve drug delivery. Cremophor EL (polyoxyl castor oil) and Tween 80 are examples of commonly used surfactants in pre-clinical formulations. A further example is the use of organic cosolvents (e.g. polyethylene glycol 400 and dimethylacetamide) to aid the solubilization of drugs during the drug discovery phase [9]. The underlisted formulations are strategies that have been employed to improve drug delivery for bedaquiline.

Poloxamer *in situ* forming gels: Bedaquiline has very low water solubility (0.000193 mg/mL), high lipophilicity (logP 7.1), T_{max} = 5hrs after oral dose, terminal $T_{1/2}$ = 5.5 months [7]. These properties make it a candidate for Long-acting injectables (LAIs) containing *in situ* forming gels. Lipophilic solutions and *in situ* forming gels with the dissolved drug have a cost advantage as they may be sterilized at the thermal filtration stage [59].

Poloxamers consists of copolymers of hydrophilic ethylene oxide (EO) and hydrophobic propylene oxide (PO), having a triblock (EO_x–PO_y–EO_x) structure arrangement, commonly used grades include P188, P237, P338, and P407. They are widely used as emulsifiers, wetting, solubilizers, and dispersing agents. Also, when dissolve in water, they exhibit reversible thermo-responsive gelling properties [60]. At levels above the CMC and critical micelle temperatures, poloxamers aggregate and form micelles due to dehydration of the hydrophobic PO block. With further increases in temperatures (above the gel point temperature), the packed micelles form gels of concentrated poloxamer solutions [61]. These formulations of thermally-induced *in situ* forming gel systems are liquids at room temperature, but form a gel at body temperature, after injection, which makes it suitable for bedaquiline delivery [59].

Binary/ternary solid dispersion utilizing poloxamer 188 and TPGS: Solid dispersion has been employed to improve saturation solubility and increase dissolution rate by converting BCS II or IV drugs either to amorphous or microcrystalline form. This supersaturated drug delivery system usually comprises the drug dispersed in one or more inert (usually hydrophilic) carrier matrices [62]. The supersaturation system uses the "spring parachute" effect to increase apparent solubility and dissolution of the drug. The spring comes from a high-energy form of the drug as it causes solubilization at concentrations higher than that obtained at equilibrium, while the parachute effect is obtained by adding excipients that inhibit precipitation (binary solid dispersions, BSD). To inhibit the precipitation and maintain the parachute effect, a third component, polymer or surfactant is added (ternary solid dispersion, TSD) [60].

In a study, poloxamer 188 (hydrophilic polymeric carrier) was added to bedaquiline in BSD and for TSD, TPGS was used as a surfactant and stabilizer. TPGS (a soluble derivative of vitamin E) enhances permeation through the biological membrane by inhibiting P-glycoprotein (P-gp) efflux pump; this is expected to provide benefit the drug's activity against MDR-TB [60].

Examples of pharmaceutical polymers used in amorphous dispersions include hydroxy propyl methyl cellulose (HPMC), hydroxypropylmethyl cellulose acetate/succinate (HPMCAS), poly(vinylpyrrolidone) (PVP), poly (vinylpyrrolidone/vinyl acetate copolymer), hydroxypropyl methylcellulose phthalate (HPMCP), etc. While examples of surfactants that may be included in amorphous dispersions include Vitamin E polyethylene glycol 1000 succinate (D-"-tocopheryl polyethylene glycol 1000 succinate), Span 80, Tween 80, or Cremophor [6]. A commentary reviewed several papers on amorphous dispersion formulations and recommended an understanding of the role GI physiological factors may play in optimizing the use of amorphous solid dispersion formulations [6]. Bedaquiline fumarate salt has also been formulated as *in situ* forming gels (ISG) prepared with poloxamer 338 and/or poloxamer 407 in N-methyl-2-pyrrolidone/water mixtures. The invitro and invivo results from rats used in this study suggested that using their optimized formulation yielded a T_{max} at 6hrs after intramuscular administration of the gel [59]. Similar research presented the fumarate salt as another ISG from a 50/50 or 75/25 ratio of poly(d,l-lactide) (PDLLA) or poly(d,l-lactide-co-glycolide) (PLGA) with a lactide/glycolide, and proposed the formulation as a possible parenteral administration for bedaquiline [63].

Lipid nanoparticles and chitosan nanocapsules: Nanomaterials are small-sized, so they can easily reach cellular levels. Their high surface area also increases their target cells' interactions, as well as their ability to be structurally and functionally modified to control their biodistribution. These physicochemical properties of nanomaterials have been used to improve the aqueous solubility of poorly soluble drugs. It can increase the local concentration of the drug, enabling lower doses in general circulation. Two bedaquiline-loaded nanocarriers were developed, nanoemulsion-based chitosan nanocapsules (CS-NC). The first consists of an oily core and a nanogel polysaccharides shell grafted (or not) with polyethylene glycol molecules. The second, lipid nanoparticles (LNPs), has a lipid core of long chains triglycerides, surrounded by a surfactant shell made of a polyethylene glycol-based surfactant, phospholipids [64]. In both cases, cationic lipids coverings were added to confer them a cationic character, and the polymeric coating for stabilization.

Bioavailability of bedaquiline tablets suspended in water: A study investigated the bioavailability of a formulation that made a suspension of bedaquiline from the tablets, for pediatric use. The study evaluated the bioequivalence of bedaquiline tablets swallowed whole vs. suspended in water. The randomized, open-label, two-period cross-over study enrolled male /female participants, 18–55 years and weighed 40–90 kg. The study demonstrates that bedaquiline tablet suspension of water had equivalent bioavailability to bedaquiline administered as 100 mg tablets swallowed whole [65].

Use of cyclodextrins and bicarbonates to increase the bioavailability of bedaquiline: The use of pharmaceutical excipients has been shown to modulate the activity of drug transport across cell membranes. Complexation is the predominant mechanism used to produce a supersaturated system when cyclodextrins are utilized [6].

A WIPO Patent WO2020069138A1 described an invention that could increase the oral bioavailability of poorly soluble drugs by incorporating cyclodextrins and/or bicarbonates. The inclusion of α-Cyclodextrins (e.g. (2,3,6-tri-0-acetyl)-a-cyclodextrin, butyl-a-cyclodextrin, succinyl-a-cyclodextrin, etc.), β-cyclodextrins (e.g. hydroxypropyl^-cyclodextrin, glucosyl^-cyclodextrin, etc.), and bicarbonates (e.g. sodium and potassium bicarbonates) were shown to increase C_{max} and AUC [66].

Conclusions

Bedaquiline, a highly lipophilic antimicrobial has shown efficacy in the treatment of multi-drug resistant TB in adults. Formulations that have been used for preclinical deliveries of bedaquiline are suggested as possible strategies for improving the bioavailability of benzoate and maleate new salts for bedaquiline.

Authors' contributions

Mercy Okezue: Conceptualization, Methodology. Stephen Byrn: Supervision.

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Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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