Solid nanoparticles for oral antimicrobial drug delivery: a review

Aun Raza[1,2], Fekade Bruck Sime[1,2], Peter J. Cabot[1], Faheem Maqbool[1], Jason A. Roberts[1,2,3,4] and James Robert Falconer[1]

[1] School of Pharmacy, Pharmacy Australia Centre of Excellence, The University of Queensland, Brisbane, QLD, Australia
[2] Centre for Translational Anti-infective Pharmacodynamics, School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia
[3] Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia
[4] Department of Pharmacy, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia

Most microbial infectious diseases can be treated successfully with the remarkable array of antimicrobials current available; however, antimicrobial resistance, adverse effects, and the high cost of antimicrobials are crucial health challenges worldwide. One of the common efforts in addressing this issue lies in improving the existing antibacterial delivery systems. Solid nanoparticles (SNPs) have been widely used as promising strategies to overcome these challenges. In addition, oral delivery is the most common method of drug administration with high levels of patient acceptance. Formulation into NPs can improve drug stability in the harsh gastrointestinal (GI) tract environment, providing opportunities for targeting specific sites in the GI tract, increasing drug solubility and bioavailability, and providing sustained release in the GI tract. Here, we discuss SNPs for the oral delivery of antimicrobials, including solid lipid NPs (SLNs), polymeric NPs (PNs), mesoporous silica NPs (MSNs) and hybrid NPs (HNs). We also discussed about the role of nanotechnology in IV to oral antimicrobial therapy development as well as challenges, clinical transformation, and limitations of SNPs for oral antimicrobial drug delivery.

Introduction

Many diseases are induced by microbes and other microorganisms, including bacteria, virus, protozoa, fungi, and algae. These microbes are omnipresent [1] and, consequently, infectious diseases are very common, accounting for a significant share of the global disease burden. Lower respiratory infections alone are among the top three diseases with highest global mortality rates [2]. Since the discovery and development of penicillin, antibiotics have become the main approach to controlling such infections. Unfortunately, the increasing resistance of microorganisms to most of the commonly used antimicrobial drugs, now known as antimicrobial resistance (AMR), is preventing the treatment of many infections. The scale of this problem is also increasing. Hospital and community infections caused by both Gram-positive and Gram-negative bacteria are increasingly becoming resistant to treatment with conventional antibiotics [3]. For instance, nearly 40% of *Staphylococcus aureus* strains in hospitals are now resistant to methicillin and vancomycin (VCM) [4]. Furthermore, by 2050, AMR could affect ~230 million people annually and, between 2014 and 2050, cumulatively cost the global economy US$100 trillion [5]. Currently, ~700 000 people die each year because of AMR, and this is predicted to reach 10 million people by 2050 [5].

Although there are various reasons for the event of AMR, Fleming presciently noted one of these while accepting the Nobel Prize, namely that 'The thoughtless person playing with penicillin treatment is morally responsible for the death of man [humans] who succumbs to infection with the penicillin-resistant organism'

Corresponding author: Falconer, J.R. (j.falconer@uq.edu.au)

https://doi.org/10.1016/j.drudis.2019.01.004

[6]. There is no doubt that misuse, both under and overuse, has made a significant contribution to the emergence of AMR. Research is now looking into the prescribing guidelines, including rules such as 'finish the course', as set out by the WHO, although Llewelyn *et al*. claimed there is little evidence that an incomplete antibiotic course increases antibiotic resistance [7]. More obvious reasons include the inappropriate use of antibiotics, such as for viral infections and nonsusceptible bacteria. However, recent campaigns are reducing the use of antibiotics; for example, data from the UK showed a 2.7 million drop in the number of antibiotics prescribed in 2016 compared with 2015 [8]. Substantial research is also being conducted to establish more robust antibiotic pharmacokinetic and pharmacodynamics (PKPD) models, so that antibiotic use can be optimized and rendered more effective, improving patient outcomes and reducing AMR [9].

Moreover, a substantial decrease in research and development (R&D) of new antimicrobials is risking the reality of untreatable infections that pose a serious threat to public health. Over the past 3 years, only six new antimicrobial drugs were approved by the US Food and Drug Administration (FDA): ceftazidime/avibactam, delafloxacin, and ozenoxacin, a combination of meropenem with the β-lactamase inhibitor vaborbactam and two monoclonal antibodies, obiltoxaximab and bezlotoxumab [10]. Cognizant of this, lately there has been a resurgence of interest among academic researchers in the development of new antimicrobials and the chemical modification of existing drug entities. However, new antimicrobial drug development does not mean that there will be no emergence of microbial resistance in the future. The frequent use of broad-spectrum antimicrobials for serious infections in a hospital setting is particularly associated with an increased risk of resistance [11]. During prolonged hospital stays, in particular, the risk of acquiring resistant infection increases for each day of hospitalization [12]. One reason for prolonged hospital stays during the treatment of major infection is that most of the potent antimicrobials used for serious infection are only available as parenteral preparations because of their poor bioavailability after oral administration. Poor oral bioavailability accounts for >70% of new chemical entities (NCEs) being rejected during preclinical development [13]. Different factors, such as poor solubility, limited permeability, and metabolic stability, are responsible for inadequate bioavailability. However, once the patient improves and is able to take drugs orally, switching to oral treatment has multiple advantages, including reducing the length of their hospital stay. Therefore, developing oral formulations of such antimicrobials is warranted to enable the switch from IV to oral antimicrobial therapies [14,15].

Nanotechnology is a promising tool to address many of the challenges associated with these oral formulations and their PK. Nanoparticles (NPs) are small (10–1000 nm) and, when combined with antimicrobials, this is responsible for giving antimicrobials new properties, such as a high surface:volume area and better bioavailability. Applications of nanotechnology in medicine could bring new hope in the fight against resistant infectious diseases. In addition, nanostructured antimicrobial agents could help to decrease the adverse effects and costs associated with antimicrobials [3,13]. Research into the use of light-sensitive NPs could also offer adjuvant therapy to antibiotics [16], as could the use of tissue-specific NPs against AMR [17]. Another promising strategy has been the use of immune system-boosting stimulants, where no antibiotic is necessary [18], although these approaches are beyond the scope of the current review.

Here, we discuss challenges for oral drug delivery, formulation strategies for antimicrobial-loaded SNPs, the role of nanotechnology in IV to oral antimicrobial therapy, and the various SNPs available for the oral delivery of antimicrobials. Furthermore, we also review the potential clinical applications and limitations of antimicrobial-loaded SNPs.

Challenges for oral drug delivery

Drug delivery via the GI tract (i.e., orally) has numerous advantages, namely patient convenience, generally less expensive, and avoidance of problems related to parenteral route, such as infection risk and pain [19]. Oral drug delivery is also preferred when the site of action is within the GI tract, such as in cases of inflammatory bowel disease and colon cancer [20,21]. However, there are some chemical and biological barriers associated with this pathway that could influence the delivery of active compounds, rendering the oral route impractical [22].

Gastrointestinal tract barriers and role of SNPs

The oral route of drug administration has several disadvantages, such as poor target specificity, lack of control over drug release and GI tract barriers (chemical and biological) [19]. P-glycoprotein (P-gp) (a multidrug efflux transmembrane protein), the hepatic first pass effect, and the adverse effects associated with the high dose of drug required to reach a therapeutic level are other challenges for oral drug delivery [13,22].

However, the poor drug solubility and stability of active drug compounds in the GI tract can be overcome using nanotechnology. Orally administered nanomedicines exhibit more stability (because they are in a solid state), prolonged residence time, and potentially high drug payload across the GI tract [22]. In theory, NP formulations can also evade the active P-gp mediated efflux that limits the bioavailability of drugs. In rats, tobramycin-loaded SLNs were shown to surpass the P-gp efflux pump and tobramycin accumulation was enhanced in intestinal cells [23]. In another study, clarithromycin (CLA)-loaded SLNs exhibited an improved PK and safety profile [24] compared with conventional CLA formulations with poor bioavailability resulting from a significant hepatic first pass effect and a short half-life, which necessitate more frequent and higher doses of CLA, increasing the risk of adverse effects and, in some cases, toxic effects, such as hepatotoxicity [25,26]. These observations demonstrate that nanotechnology has potential as a useful tool to help reduce GI tract-related problems for the oral drug delivery of antibiotics.

Solid nanoparticle-based carrier systems and their applications against microbial diseases

Solid lipid nanoparticles

SLNs were first engineered by Schwarz *et al*. during the early 1990s [27]. SLNs comprise a solid lipid core surrounded by a single layer of lipid forming an outer shell (Fig. 1a). SLNs are mainly a solid lipid structure with different surfactants for emulsification. Solid lipids used for SLNs preparation include fatty acids, triglycerides,

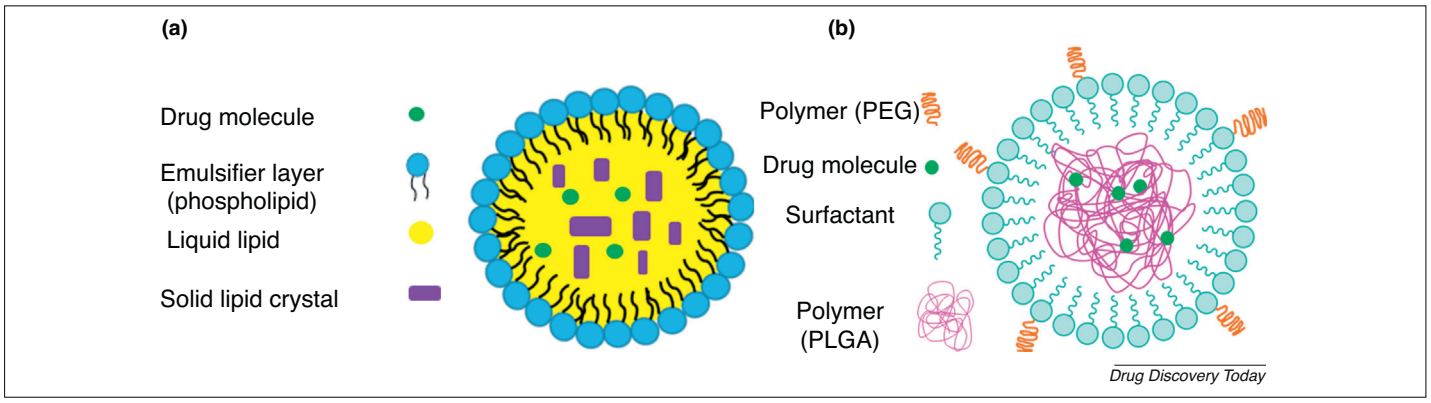

FIGURE 1

Structural representation of nanoparticles. (a) Solid lipid nanoparticle. (b) Polymeric nanoparticle. Abbreviations. PEG: polyethylene glycol; PLGA: polylactic–polyglycolic acid.

steroids, and waxes. To stabilize the lipid dispersion, soybean lecithin, phosphatidylcholine, poloxamer 188, sodium cholate, and sodium glycocholate are commonly used as emulsifiers. In terms of the particle diameter, SLNs between 50 to 1000 nm are considered to be promising for the oral delivery of different active compounds [28–31]. The benefits to the use of SLNs in oral drug delivery include bioavailability enhancement, prolonged drug release, and protection of chemically labile drugs. Moreover, SLNs prepared using generally regarded as safe (GRAS) ingredients are biocompatible and biodegradable, and exhibit low cytotoxicity to mammalian cells, all helpful features on a FDA application [32]. Herein, we focus on the development of antimicrobial SLNs for the treatment of microbial diseases.

Previous work on the orally administered antibiotic, tobramycin showed poor absorption from intestinal cells because of the P-gp efflux pump. However, incorporating tobramycin (TOB) in SLNs reduced the activity of the P-gp efflux pump and increased the absorption and infection site payload through endocytosis [23]. Similarly, the orally administered quinolone antibiotic norfloxacin (NFX) has poor permeability and low bioavailability (40%) in humans and animals [33]. Again, by incorporating NFX in a SLN, an oral drug delivery formulation was engineered that demonstrated 12-fold increases in the bioavailability and stability of the drug without any cytotoxicity [34]. CLA is also extensively used orally because of its higher stability in acidic environments and is effectively used to treat pneumonia, influenza, and other respiratory tract infections. However, CLA has low aqueous solubility, a short half-life of 3–4 h, and low oral bioavailability because of hepatic first pass metabolism. These properties limit its efficacy and frequently higher doses are needed for required therapeutic effects [25,26]. However, using CLA-loaded SLNs (CLA-SLNs) increased the maximum concentration (C_{max}) by 2.3-fold, the time to maximum concentration (T_{max}) by twofold, mean residence time by 1.4-fold, and oral bioavailability by fivefold [24]. This clearly shows the beneficial effects of combining CLA with a SLN formulation.

The reduced pharmacological effects of capsules of the broad-spectrum antifungal drug, miconazole (MN), have been reported against *Candidiasis* because of a poor water solubility of 1 μg/ml. Thus, MN-SLNs as oral formulation were developed to address the issue [35]. Investigations revealed that MN-SLNs enhanced the oral bioavailability (2.5-fold) and antifungal activity of MN against candidiasis compared with MN capsules [36].

Isoniazid (IN) is used to treat different types of TB. However, the short half-life (1–4 h) of IN in plasma demands frequent higher doses that could cause hepatotoxicity and neurotoxicity. IN-SLNs for oral delivery were engineered and their PK studied in rats. Results showed that oral administration of IN-SLNs in rats improved the relative bioavailability in plasma (sixfold) and brain (fourfold) with respect to free IN at a similar dose of 25 mg/kg [37]. Lopinavir (LN) is an antiretroviral drug with low therapeutic efficacy because of poor aqueous solubility, the P-gp efflux pump, and hepatic first pass metabolism. LN-loaded SLNs with stearic acid as a solid lipid were investigated and showed higher oral bioavailability (2.5-fold) and more stability compared with free drug [38]. In another study, LN-loaded SLNs with the constituent compritol 888 ATO as the solid lipid were prepared. The study showed that LN-SNPs suppressed the P-gp efflux pump and improved C_{max} (4.9-fold) and oral bioavailability (3.6-fold) with respect to free drug [39]. Efavirenz (EZ) is another antiretroviral drug with poor oral bioavailability and stability. A study of EZ incorporated into SLNs observed the enhanced oral bioavailability of EZ. The good stability of EZ-SNPs for 6 months at 40 °C was also reported. Furthermore, oral administration of EZ-SLNs revealed significant enhancement in C_{max} (5.3-fold) and bioavailability (11-fold) [40]. Examples of SLNs based antimicrobials are summarized in Table 1.

Polymeric nanoparticles

In 1976, Langer and Folkman reported the first polymer-based drug delivery systems (DDSs) [41]. There are three properties of PNs (Fig. 1b) that could be helpful for antimicrobial drug delivery. First, polymeric nanostructures have good stability. Second, during PN synthesis, their different particle characteristics, such as size, zeta potential, and drug release, can be changed by using different polymers with different length and surfactants. Third, surface modification of PN functional groups with active compounds or targeting ligands could improve targeted antimicrobial drug delivery [42]. PNs are being investigated for antimicrobial drug delivery to treat different infections with enhanced therapeutic effects. Herein, we focus on reports of the development of PNs with antimicrobials for microbial diseases.

TABLE 1

SLNs and PNs for antimicrobial drug delivery

Active compound	Formulation excipient	Method of preparation	Particle Size (nm) ± S.D	Encapsulation efficiency (wt %)	Drug loading content (wt %)	Advantage	Refs
SLNs							
TOB	Stearic acid, Epikuron 200 (surfactant), Tauro-cholate (co-surfactant)	Microemulsion	85 ± 5	Not shown	2.5	Suppresses P-gp efflux pump, increases absorption and payload of tobramycin	[23]
NFX	Stearic acid (as lipid matrix), polyvinyl alcohol (surfactant)	Hot homogenization and ultrasonication	301 ± 16.64	92.35 ± 2.24	8.58 ± 0.21	Enhanced oral bioavailability and drug stability	[34]
CLA	Stearic acid and tristearin (lipid matrix), pluronic F-68 (surfactant)	Emulsification solvent evaporation	307 ± 23	84 ± 9	6.5 ± 0.9	Increased C_{max} and oral bioavailability	[24]
MN	Precirol ATO 5 (lipid mixture), Lecinol (emulsifier) Cremophor RH40 (surfactant)	hot homogenization and/or ultrasonication	23	90.2	Not shown	Enhanced oral bioavailability and antifungal activity	[36]
IN	Compritol 888 ATO and stearic acid, polysorbate 80, soy lecithin	Microemulsification	48.4	69	>92	Improved relative bioavailability in plasma and brain	[37]
LN	Stearic acid, Poloxamer 407 (P407) and PEG 4; glyceryl behenate, P407, PEG 4000	Hot self nanoemulsification	180.6 ± 2.32; 214.5 ± 4.07	91.5 ± 1.3; 81.6 ± 2.3	50.83 ± 0.72; 13.06 ± 0.93	Enhanced oral bioavailability	[38,39]
EZ	Glyceryl monostearate (lipid matrix), Tween 80 (surfactant)	Hot homogenization and/or ultrasonication	124.5 ± 3.2	86 ± 1.03	Not shown	Increased C_{max} and bioavailability	[40]
PNs							
AMB	PEGylated PLGA-PEG	Quadeib *et al.* (modified)	25.3 ± 2.7	56.5 ± 3.9	Not shown	Improved oral absorption and bioavailability	[51]
SM	Dextran sulfate, chitosan, tripolyphosphate (TTP); PLG	TTP; multiple emulsions	492.23 ± 27.03; 153.12	51.69 ± 1.29; 32.12 ± 4.08	58.81 ± 2.50 14.28 ± 2.83	Orally administered NPs showed equal efficacy with subcutaneous dose; eight orally administered doses of NPs had equal efficacy	[44]
CLO	PLG; alginate	Multiple emulsions and/or solvent evaporation; cation-induced controlled gelification	217; 235	48.33 ± 5.21; 90 ± 3	Not shown	Controlled drug release and improved bioavailability	[52]
ECO	PLG; alginate	Multiple emulsions and/or solvent evaporation; cation-induced controlled gelification	217; 235	52.27 ± 3.8; 95 ± 2.5	Not shown	Controlled drug release and improved bioavailability	[52]

The antibiotics aminoglycosides (AG) have poor oral absorption and, therefore, are mostly administered via the parenteral route. Moreover, ototoxicity and nephrotoxity are commonly observed adverse effects related to their use if the doses are not monitored properly [43]. Lu *et al*. developed streptomycin (SM)-loaded chitosan (CHT) NPs and investigated their *in vivo* oral activity in a mouse model of chronic TB infection. *In vivo* data revealed that orally administered SM-NPs had equal efficacy with respect to subcutaneously (SC) administered SM at the same dose concentration (100 mg ml^{-1}) [44]. In another study, SM-loaded PLG NPs (SM-PLG-NPs) were developed and evaluated in mice after oral administration. It was observed that SM-PLG-NPs were responsible for the sustained release of drug with higher bioavailability (21-fold) compared with single drug administration. Moreover, eight doses of SM-PLG-NPs administered orally over the course of a week had similar efficacy with respect to 24 doses of SM administered intramuscularly (IM) to *Mycobacterium tuberculosis* H37Rv-infected mice [45]. Anti-TB drugs (ATDs) are used to treat cerebral TB. However, ATDs are regularly administered for a long period of time [46]. A recent study evaluated the efficient cerebral drug delivery of ATDs [rifampicin (RIF) + IN + pyrazinamide (PZA) + ethambutol (EMB)] loaded with PLG-NPs. These ATDs-PLG-NPs were administered orally to mice for PK and chemotherapeutic investigations. A single oral dose of these NPs exhibited sustained release of drug in plasma (5–8 days) and brain (9 days). Furthermore, five doses of NPs orally administered to *M. tuberculosis* H37Rv-infected mice (every 10th day) resulted in undetectable bacilli in the meninges. These results indicated that PNs have potential for the cerebral drug delivery of ATDs [47]. In another study, PNs of ATDs, such IN, RIF, PZA, and EMB, using alginate were prepared and orally administered to mice for PK evaluation. Free drugs were orally administered to mice at equivalent doses for a comparison study. It was observed that the oral bioavailability for all encapsulated drugs was higher compared with free drugs [48].

Amphotericin B (AMB) is an antifungal drug that is mostly used to treat leishmaniasis. However, it has poor aqueous solubility parenterally as well as nephrotoxicity and hematological adverse effects [49,50]. Multiple doses of AMB in PEGylated polylactic-polyglycolic acid copolymer (PLGA-PEG) NPs s were orally administered to rats for 1 week, with no resulting nephrotoxicity. The authors did not report any hematological adverse effects. Moreover, significant enhancement of NP bioavailability was observed with respect to AMB. Furthermore, adding 2% w/w glycyrrhizic acid (GA) into the NP formulation enhanced the bioavailability from 1% to 10.5% [51].

In another study, the oral bioavailability of two antifungal drugs, clotrimazole (CLO) and econazole (ECO), was investigated. Two polymeric formulations using PLG and alginate were developed for both drugs and orally administered to mice to evaluate their PK. The study showed the controlled release of the drugs for 5–6 days using the nanoformulations, whereas uncapsulated drugs were cleared after 3–4 h following oral and/or IV administration. Moreover, bioavailability also improved and drugs could be detected in organs such as spleen, lungs and liver after 6–8 days, whereas single drugs were cleared within 12 h [52]. Examples of PN-based antimicrobials are summarized in Table 1.

Mesoporous silica nanoparticles

MSNs (Fig. 2a) have several advantages over traditional nanocarriers that make them superior to such carriers, including easy synthesis, versatile surface chemistry, functionalization, and biocompatibility [22,53]. MSNs also have a high surface:volume area and pore-volume ratio that can exceed 1000 m^2/g and 0.5–1 cm^3/g, respectively [54]. Both these features could facilitate high drug loading. For example, multifunctional MSNs of IN and PZA show 40% and 35% drug loading capacity, respectively [55]. Thus, having a larger surface:volume ratio is an obvious way to improve drug loading that could enhance oral drug delivery.

Furthermore, MSNs have also been investigated for enhancing the oral bioavailability of poorly water-soluble drugs. Given their inorganic skeleton, MSNs could increase the stability of active compounds in the higher thermal and acidic environment of the GI tract [56]. In addition, the high surface:volume ratio and large pore volume of MSNs also enable them to deliver a large number of active molecules into different organs and tissues [22]. The functionalization or coating of MSNs with organic groups and/or functionalities (e.g., amino/phosphonate groups or pH-sensitive biomolecules) can control premature drug release in the GI tract and provide high doses of active compounds in different organs and tissues [57]. The major drawback of MSNs is that there is currently no FDA-approved product that uses MSNs. Silica is classified as generally recognized as safe (GRAS) by the FDA and is added to food and cosmetics [58]. MSNs break down into water-soluble orthosilicic acid [$Si(OH)_4$] and *in vitro* studies show no toxicity up to 100 mg/ml in cell culture [59]. It is well known that cell membrane also comprises lipids (phosphatidylcholine); therefore, coating of MSNs with such lipids could help to improve their profile and regulatory acceptability [60,61].

Studies have encapsulated antimicrobials with MSNs with enhanced PK and therapeutic effects [62–65]. Polymyxin B (PLX) is mostly used against antibiotic-resistant Gram-negative bacteria. However, because of its toxic effects, its clinical use is limited. PLX-loaded MSNs were developed to overcome problems associated with PLX and to improve its therapeutic properties. The resulting MSNs showed enhanced antibacterial activity, controlled release of drug, and decreased cytotoxicity that resulted from the prevention of reactive oxygen species (ROS) generation [66]. In another study, CLA was loaded into amine functionalized MSN (MSNs-NH_2) that were found to have higher antibacterial activity against *S. aureus* and *Escherichia coli* compared with single drug. Moreover, a pH-sensitive drug release profile of CLA/MSN-NH_2 was also observed [67]. Ciprofloxacin (CF)-loaded lipid-coated MSNs (L-MSNs) were engineered for the oral delivery of CF. *In vitro* assays showed the higher antibacterial activity of CF-L-MSN_S compared with single drug. Moreover, MSNs provided higher site payload of drug within infected cells and eradicated pathogens from mice after oral drug delivery [68]. Other antimicrobials, such as erythromycin and VCM, have also been encapsulated within MSNs and their enhanced antibacterial activities reported [69,70]. Examples of MSN-based antimicrobials are summarized in Table 2.

Hybrid nanoparticles

DDSs are considered more efficient over traditional drug therapy because of several advantages, including better therapeutic efficacy because of a prolonged drug release profile, higher drug entrap-

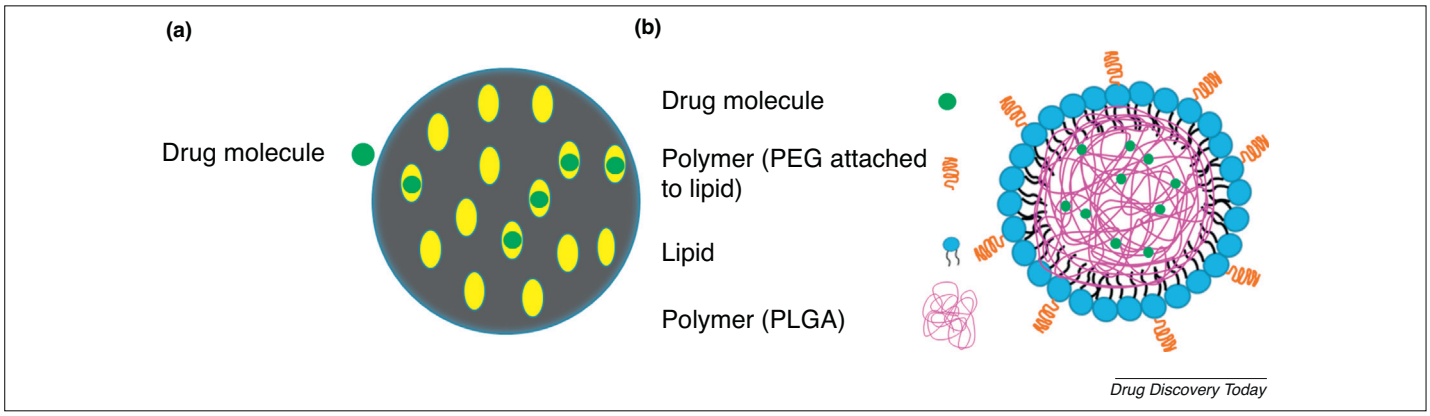

FIGURE 2

Structural representation of nanoparticles. (a) Mesoporous silica nanoparticle. (b) Hybrid nanoparticle. Abbreviations. PEG: polyethylene glycol; PLGA: polylactic-polyglycolic acid.

ment, and decreased drug adverse effects and toxicity, usually because less drug is required to bring about a desired therapeutic effect. However, there is no ideal or perfect carrier for drug delivery because of limitations including poor drug loading or encapsulation and loading efficiency, poor drug targeting, and thermal and/or chemical instability. Hence, biohybrid systems have been developed to overcome these problems [71]. In biohybrid systems, biohybrid materials are used that combine particular characteristics of organic nanocarriers with the adhesiveness and biodegradability of (bio)polymers [72]. Polymer–protein and lipid polymer HNs (PPNs; Fig. 2 b) have been reported [71,73].

PPNs result in different PK and PD properties of drugs [74]. For example, cefpirome (CP) is a cephalosporin antibiotic that is used against Gram-positive and Gram-negative bacteria. It has low aqueous solubility and poor bioavailability [75]. To overcome these PK problems, frequent high doses of CP are used, but result in adverse, even toxic, effects. To overcome these issues, CP was loaded into phycocyanin functionalized ovalbumin (OVA) NPs that released the drug in a controlled manner and had improved antibacterial activity against human pathogenic bacteria [76]. However, SLNs still have limitations, such as low expulsion of drug time and low capability to encapsulate either drugs with cation charge or hydrophilic drugs [77–79]. To overcome these problems with SLNs, hybridization of SLNs with biomaterials such as polymers is another important technique. Such biohybridization produces electrostatic and hydrogen interactions among the excipients and improves properties of SLNs including the drug release profile, permeation, and therapeutic efficacy [78,80,81]. For example, the cationic charge of PLX limits its efficient loading into SLNs. Therefore, researchers first conjugated PLX with sodium alginate (SA) and was then loaded into SLNs, which showed the efficient drug loading of PLX with improved antibacterial activity [82].

Lipid–polymer HNs (LPNs) also show improved PK and PD properties over PNs. LPNs of VCM were developed with co-excipients such as glyceryl tripalmitate (lipid) and eudragit RS100 (polymer). Improved encapsulation efficiency (from 27.8% to 41.5%, 54.3%, and 69.3%) was observed with the addition of oleic

TABLE 2

Mesoporous SLNs and HNs for antimicrobial drug delivery

Active compound	Formulation	Advantage	Refs
MSNs			
PLX	Bare MSNs (B-MSNs); aminated MSNs (N-MSNs); carboxyl functionalized MSNs (C-MSNs)	Enhanced antibacterial activity; reduced cytotoxicity effects of drug	[66]
CLA	Amine functionalized MSNs (MSN-NH_2)	Improved antimicrobial activity; pH-sensitive drug release kinetics	[67]
CF	L-MSNs	Improved antibacterial activity; low dose requirement for oral drug delivery	[68]
HNs			
CP	Phycocyanin functionalized ovalbumin NPs	High spectrum of antibacterial activity; controlled drug release profile	[76]
PLX	SA–cross-linked SLNs	Enhanced antibacterial activity compared with free antibiotic	[82]
VCM	Lipid–polymer (glyceryl tripalmitate – Eudragit RS100) HNs	Enhanced antibacterial activity; sustained release of drug	[83]
AMB	Lipid–polymer (lecithin-gelatin) HNs	Improved oral bioavailability of drug and enhanced therapeutic efficacy	[84]

acid (OA), CHT, and SA, respectively. All the formulations showed better antibacterial activity against methicillin-resistant *S. aureus* (MRSA) compared with a single drug (VCM) [83].

Although research on hybrid nanoformulations of antimicrobials has increasing in recent years, most publications report *in vitro* activity and there are few report of the oral delivery of antimicrobials. For example, AMB-loaded PLNs (AMB-PLNs) with lecithin and gelatin were developed to enhance the oral bioavailability of AMB, resulting in controlled drug release kinetics. A PK study revealed that there was significant enhancement in oral bioavailability (4.69-fold) of AMB-PLNs compared with free drug [84]. Examples of HN-based antimicrobials are summarized in Table 2.

Role of nanotechnology in IV to oral antimicrobial therapy development

Many antimicrobials, such as carbapenems and AG have poor oral bioavailability and can only be given via injectable routes because they are inactive after oral administration [13,85]. Such administration can have serious complications, such as thrombophlebitis, catheter-related problems (i.e., bloodstream infections and phlebitis) as well as being time consuming and expensive. Where oral formulations are available, IV–oral switch therapy of antimicrobials can be important for clinically stable patients because it can reduce their stay in hospital and associated costs. Switching of IV–oral antibiotics is possible for ~40–50% of patients 2–3 days after their IV treatment [86]. Metronidazole, levofloxacin, linezolid, fluconazole, and Iitraconazole are antimicrobials included in the IV–oral switch program [15,87]. Some IV medications provide maximum bioavailability with greater effects, but there are some oral antibiotics with comparable bioavailability (e.g., levofloxacin provides ≥99% oral bioavailability) to that of the parenteral form of antibiotics [15]. However, there are many powerful antimicrobials that are too difficult (perhaps impossible) to formulate into oral dosage forms using conventional strategies. Therefore, nanotechnology could be important in IV–oral switch programs through the development of oral nanoformulations of IV antimicrobials.

AGs are highly polar and/or hydrophilic (water soluble) compounds that are poorly absorbed from the GI tract. An oral nanoformulation of injectable SM enhanced the relative bioavailability of SM 21-fold compared with intramuscular free drug [45]. Carbapenem antibiotics (meropenem, imipenem, etc.) are administered by injection, because the hydrophilic nature, gastric pH and secretory transport of the small intestine result in inactive meropenem following oral administration [85]. Moreover, the short circulation half-life of meropenem also means that high frequent doses are required (0.5–1 g, three times daily) [88]. Meropenem-loaded CHT and SLNs have been reported, with *in vitro* evaluations of drug-loaded NPs showing higher antimicrobial activity compared with free drug [89,90]. Although research is required to successfully modify injectable antimicrobials for oral drug delivery, nanotechnology could have a key role in this transformation.

Clinical transformation, safety considerations, and limitations

Nanodrug development has received significant attention over the past decade. Clinically, dozens of nanoformulations have received FDA approval, and many are in early stages of development or in clinical trials. The amount of work occurring in this field predicts that many new nanodrugs will become available for clinical use [91,92]. From 1995 to 2017, the FDA approved 51 nanomedicines and another 77 are in clinical trials. Indeed, 40% of clinical trials for nanomedicines are started over the past 5 years [93].

FDA-approved nanomedicines are mostly polymeric and liposomal formulations, but other inorganic and metallic NPs are also in clinical trials. For example, two FDA-approved polymeric nanomedicines, Pegasys (pegylated IFN alpha-2a) and PegIntron (pegylated IFN alpha-2b) are used to treat hepatitis B and hepatitis C, respectively. FDA-approved antimicrobials, such as liposomal AMB lipid complex and liposomal AMB, are also available on the market to treat fungal infections [93]. Most drugs in clinical trials are anticancer and antimicrobial nanodrugs [91,93]. Therefore, many antimicrobial nanomedicines could also become available in the near future. Doxycycline PNs are in Phase II trials for use against chronic periodontitis. Two other antimicrobial polymeric nanoformulations of EZ and LN are also in Phase I trials to treat HIV [92].

Nanomedicines have several benefits, one of them is to reduce the toxicity of drugs. However, we cannot make a general statement about the safety of nanomedicines because comprise different types of material [94]. In addition, studies have also demonstrated that NPs circulate throughout the body and could result in toxicity. Several reports are shown that the oxidative activity and immune response of NPs can cause genotoxicity and inflammation of liver and lungs. Different strategies, such as surface modification of NPs, can be used to reduce such toxicity [95]. Therefore, such limitations associated with nanomedicines must be overcome to improve these technologies. For oral nanodrug delivery, more research is required to differentiate the conditions of the GI tract in animal and human models to provide more reliable information for translation studies.

Concluding remarks and perspectives

Nanotechnology has emerged as an advanced technique to overcome limitations associated with current antimicrobial therapies. Several limitations of antimicrobials, such as poor stability, burst or premature drug release, enzyme degradation, microbial resistance, and cytotoxicity, restrain their clinical use. Several factors, such as poor targeted antimicrobial delivery, frequent higher doses, adverse effects, and slow development of new antimicrobials, require novel solutions. Nanotechnology has an important role in improving the PK profile of these drugs and to make them useful clinically. Most new chemical entities (70%) and commercial drugs (40%) for oral use are poorly soluble in water. Given the increased research interest, several nanomedicines have been developed with low toxicity and improved efficacy in recent years. Thus, efforts should focus not only on the laboratory synthesis and/or functionalization of SNPs, but also on further improvement of the targeting ability of orally administrated SNPs via their increased penetration through the different barriers (e.g., intestinal epithelial layer or mucus), leading to higher uptake from the GI tract. Although significant progress has resulted in the development of antimicrobial nanodrugs, research gaps remain. Moreover, nanodrugs might be helpful for developing

oral dosage forms for many antimicrobials that are available only in injectable form. Thus, there is much work ahead to successfully translate this new family of DDSs from the laboratory into marketable healthcare products.

Acknowledgment

A.R. is a recipient of Australian Government Research Training Program Scholarship from The University of Queensland, Brisbane, Australia, for which we are very grateful.

References

1 Singh, S.R. *et al.* (2014) A review on recent diseases caused by microbes. *J. Appl. Environ. Microbiol.* 2, 106–115
2 Murdoch, D.R. and Howie, S.R. (2018) The global burden of lower respiratory infections: making progress, but we need to do better. *Lancet Infect. Dis.* 18, 1162–1163
3 Sharma, A. *et al.* (2012) *Nanotechnology for Targeted Drug Delivery to Combat Antibiotic Resistance*. Taylor & Francis
4 Cohen, M.L. (2000) Changing patterns of infectious disease. *Nature* 406, 762
5 O'Neill, J. (2015) *Tackling a Global Health Crisis: Initial Steps*. AMR
6 Fleming, A. (1945) Penicillin's finder assays its future. *New York Times* 26, 21
7 Llewelyn, M.J. *et al.* (2017) The antibiotic course has had its day. *BMJ* 358, j3418
8 Knapton, S. (2016) Human embryos kept alive in lab for unprecedented 13 days so scientists can watch development. *The Telegraph* May 4
9 Udy, A.A. *et al.* (2018) *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*. Springer
10 Andrei, S. *et al.* (2018) New FDA approved antibacterial drugs: 2015–2017. *Discoveries* 6, 10
11 Llor, C. and Bjerrum, L. (2014) Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther. Adv. Drug Saf.* 5, 229–241
12 Hassan, M. *et al.* (2010) Hospital length of stay and probability of acquiring infection. *Int. J. Pharm. Healthc. Market.* 4, 324–338
13 Date, A.A. *et al.* (2016) Nanoparticles for oral delivery: design, evaluation and state-of-the-art. *J. Control. Release* 240, 504–526
14 Cunha, B.A. (2001) Intravenous to oral antibiotic switch therapy. *Drugs Today* 37, 311–320
15 Cunha, B.A. (1997) Intravenous-to-oral antibiotic switch therapy: a cost-effective approach. *Postgrad. Med.* 101, 111–128
16 Anon (2017) *Light-Activated Nanoparticles Can Supercharge Current Antibiotics*. EurekAlert
17 Hussain, S. *et al.* (2018) Antibiotic-loaded nanoparticles targeted to the site of infection enhance antibacterial efficacy. *Nat. Biomed. Eng.* 2, 95
18 Cheng, G. *et al.* (2014) Antibiotic alternatives: the substitution of antibiotics in animal husbandry? *Front. Microbiol.* 5, 217
19 Ensign, L.M. *et al.* (2012) Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. *Adv. Drug Deliv. Rev.* 64, 557–570
20 Nguyen, C.T. *et al.* (2017) Bifunctional succinylated ε-polylysine-coated mesoporous silica nanoparticles for pH-responsive and intracellular drug delivery targeting the colon. *ACS Appl. Mater. Interfaces* 9, 9470–9483
21 Hua, S. *et al.* (2015) Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: selective targeting to diseased versus healthy tissue. *Nanomedicine* 11, 1117–1132
22 Florek, J. *et al.* (2017) Evaluation of mesoporous silica nanoparticles for oral drug delivery–current status and perspective of MSNs drug carriers. *Nanoscale* 9, 15252–15277
23 Bargoni, A. *et al.* (2001) Transmucosal transport of tobramycin incorporated in solid lipid nanoparticles (SLN) after duodenal administration to rats. Part II—tissue distribution. *Pharmacol. Res.* 43, 497–502
24 Sharma, M. *et al.* (2016) Implications of designing clarithromycin loaded solid lipid nanoparticles on their pharmacokinetics, antibacterial activity and safety. *RSC Adv.* 6, 76621–76631
25 Inoue, Y. *et al.* (2007) Application of ascorbic acid 2-glucoside as a solubilizing agent for clarithromycin: solubilization and nanoparticle formation. *Int. J. Pharm.* 331, 38–45
26 Rodvold, K.A. (1999) Clinical pharmacokinetics of clarithromycin. *Clin. Pharm.* 37, 385–398
27 Schwarz, C. *et al.* (1994) Solid lipid nanoparticles (SLN) for controlled drug delivery. I. Production, characterization and sterilization. *J. Control. Release* 30, 83–96
28 Rostami, E. *et al.* (2014) Drug targeting using solid lipid nanoparticles. *Chem. Phys. Lipids* 181, 56–61
29 zur Mühlen, A. *et al.* (1998) Solid lipid nanoparticles (SLN) for controlled drug delivery: drug release and release mechanism. *Eur. J. Pharm. Biopharm.* 45, 149–155
30 Zhang, L. *et al.* (2010) Development of nanoparticles for antimicrobial drug delivery. *Curr. Med. Chem.* 17, 585–594
31 Geszke-Moritz, M. and Moritz, M. (2016) Solid lipid nanoparticles as attractive drug vehicles: composition, properties and therapeutic strategies. *Mater. Sci. Eng. C* 68, 982–994
32 Lin, C.-H. *et al.* (2017) Recent advances in oral delivery of drugs and bioactive natural products using solid lipid nanoparticles as the carriers. *J. Food Drug Anal.* 25, 219–234
33 Gips, M. and Soback, S. (1996) Norfloxacin nicotinate pharmacokinetics in unwearied and weaned calves. *J. Vet. Pharmacol. Ther.* 19, 130–134
34 Dong, Z. *et al.* (2011) Preparation and *in vitro*, *in vivo* evaluations of norfloxacin-loaded solid lipid nanoparticles for oral delivery. *Drug Deliv.* 18, 441–450
35 Mendes, A. *et al.* (2013) Miconazole-loaded nanostructured lipid carriers (NLC) for local delivery to the oral mucosa: improving antifungal activity. *Colloids Surf. B Biointerfaces* 111, 755–763
36 Aljaeid, B.M. and Hosny, K.M. (2016) Miconazole-loaded solid lipid nanoparticles: formulation and evaluation of a novel formula with high bioavailability and antifungal activity. *Int. J. Nanomed.* 11, 441
37 Bhandari, R. and Kaur, I.P. (2013) Pharmacokinetics, tissue distribution and relative bioavailability of isoniazid-solid lipid nanoparticles. *Int. J. Pharm.* 441, 202–212
38 Negi, J.S. *et al.* (2013) Development of solid lipid nanoparticles (SLNs) of lopinavir using hot self nano-emulsification (SNE) technique. *Eur. J. Pharm. Sci.* 48, 231–239
39 Negi, J.S. *et al.* (2014) Development and evaluation of glyceryl behenate based solid lipid nanoparticles (SLNs) using hot self-nanoemulsification (SNE) technique. *Arch. Pharm. Res.* 37, 361–370
40 Gaur, P.K. *et al.* (2014) Enhanced oral bioavailability of efavirenz by solid lipid nanoparticles: *in vitro* drug release and pharmacokinetics studies. *BioMed Res. Int* 2014 Article ID 363404, 9 pages
41 Langer, R. and Folkman, J. (1976) Polymers for the sustained release of proteins and other macromolecules. *Nature* 263, 797
42 Venugopal, J. *et al.* (2009) Continuous nanostructures for the controlled release of drugs. *Curr. Pharm. Des.* 15, 1799–1808
43 Forge, A. and Schacht, J. (2000) Aminoglycoside antibiotics. *Audiol. Neurotol.* 5, 3–22
44 Lu, E. *et al.* (2009) Preparation of aminoglycoside-loaded chitosan nanoparticles using dextran sulphate as a counterion. *J. Microencapsul.* 26, 346–354
45 Pandey, R. and Khuller, G.K. (2007) Nanoparticle-based oral drug delivery system for an injectable antibiotic: streptomycin. *Chemotherapy* 53, 437–441
46 Katti, M.K. (2004) Pathogenesis, diagnosis, treatment, and outcome aspects of cerebral tuberculosis. *Med. Sci. Monit.* 10, RA215–RA229
47 Pandey, R. and Khuller, G. (2006) Oral nanoparticle-based antituberculosis drug delivery to the brain in an experimental model. *J. Antimicrob. Chemother.* 57, 1146–1152
48 Ahmad, Z. *et al.* (2006) Pharmacokinetic and pharmacodynamic behaviour of antitubercular drugs encapsulated in alginate nanoparticles at two doses. *Int. J. Antimicrob. Agents* 27, 409–416
49 Chuealee, R. *et al.* (2011) Bioactivity and toxicity studies of amphotericin B incorporated in liquid crystals. *Eur. J. Pharm. Sci.* 43, 308–317
50 Cifani, C. *et al.* (2012) Commercially available lipid formulations of amphotericin B: are they bioequivalent and therapeutically equivalent? *Acta Biomed.* 83, 154–163
51 Radwan, M.A. *et al.* (2017) Oral administration of amphotericin B nanoparticles: antifungal activity, bioavailability and toxicity in rats. *Drug Deliv.* 24, 40–50
52 Pandey, R. *et al.* (2005) Nano-encapsulation of azole antifungals: potential applications to improve oral drug delivery. *Int. J. Pharm.* 301, 268–276
53 Mekaru, H. *et al.* (2015) Development of mesoporous silica-based nanoparticles with controlled release capability for cancer therapy. *Adv. Drug Deliv. Rev.* 95, 40–49
54 Tarn, D. *et al.* (2013) Mesoporous silica nanoparticle nanocarriers: biofunctionality and biocompatibility. *Acc. Chem. Res.* 46, 792–801
55 Shen, S. *et al.* (2017) High drug–loading nanomedicines: progress, current status, and prospects. *Int. J. Nanomed.* 12, 4085
56 Hata, H. *et al.* (1999) Adsorption of taxol into ordered mesoporous silicas with various pore diameters. *Chem. Mater.* 11, 1110–1119
57 Mehmood, A. *et al.* (2017) Mesoporous silica nanoparticles: a review. *J. Dev. Drugs* 6, 1000174

58 US Department of Health and Human Services (2015) *US Food and Drug Administration: GRAS Substances (SCOGS) Database*. US Department of Health and Human Services
59 Watermann, A. and Brieger, J. (2017) Mesoporous silica nanoparticles as drug delivery vehicles in cancer. *Nanomaterials* 7, 189
60 Zhang, X. *et al.* (2014) Biofunctionalized polymer-lipid supported mesoporous silica nanoparticles for release of chemotherapeutics in multidrug resistant cancer cells. *Biomaterials* 35, 3650–3665
61 Ramishetti, S. and Huang, L. (2012) Intelligent design of multifunctional lipid-coated nanoparticle platforms for cancer therapy. *Ther. Deliv.* 3, 1429–1445
62 Lin, V. *et al.* (2006) Inventors; Iowa State University Research Foundation (ISURF), assignee. Antimicrobial mesoporous silica nanoparticles. United States patent application US 10/945,545.
63 González, B. *et al.* (2018) Mesoporous silica nanoparticles decorated with polycationic dendrimers for infection treatment. *Acta Biomater.* 68, 261–271
64 Seneviratne, C.J. *et al.* (2014) Nanoparticle-encapsulated chlorhexidine against oral bacterial biofilms. *PLoS One* 9, e103234
65 Xu, J. *et al.* (2017) Antibacterial activity of N-halamine decorated mesoporous silica nanoparticles. *J. Phys. Chem. Solids* 108, 21–24
66 Gounani, Z. *et al.* (2018) Loading of polymyxin B onto anionic mesoporous silica nanoparticles retains antibacterial activity and enhances biocompatibility. *Int. J. Pharm.* 537, 148–161
67 Khosravian, P. *et al.* (2018) Enhancement antimicrobial activity of clarithromycin by amine functionalized mesoporous silica nanoparticles as drug delivery system. *Lett. Drug Des. Discov.* 15, 787–795
68 Mudakavi, R.J. *et al.* (2014) Lipid coated mesoporous silica nanoparticles as an oral delivery system for targeting and treatment of intravacuolar *Salmonella* infections. *RSC Adv.* 4, 61160–61166
69 Pourjavadi, A. and Tehrani, Z.M. (2014) Mesoporous silica nanoparticles (MCM-41) coated PEGylated chitosan as a pH-responsive nanocarrier for triggered release of erythromycin. *Int. J. Polym. Mater. Polym. Biomater.* 63, 692–697
70 Qi, G. *et al.* (2013) Vancomycin-modified mesoporous silica nanoparticles for selective recognition and killing of pathogenic gram-positive bacteria over macrophage-like cells. *ACS Appl. Mater. Interfaces* 5, 10874–10881
71 Ribeiro, L.N. *et al.* (2017) Advances in hybrid polymer-based materials for sustained drug release. *Int. J. Polym. Sci.* 2017 Article ID 1231464, 16 pages
72 Moghanjoughi, A.A. *et al.* (2016) A concise review on smart polymers for controlled drug release. *Drug Deliv. Transl. Res.* 6, 333–340
73 Wakaskar, R.R. (2018) General overview of lipid–polymer hybrid nanoparticles, dendrimers, micelles, liposomes, spongosomes and cubosomes. *J. Drug Target.* 26, 311–318
74 Zhao, W. *et al.* (2015) Synthesis of well-defined protein–polymer conjugates for biomedicine. *Polymer* 66, A1–A10
75 Garau, J. *et al.* (1997) Fourth-generation cephalosporins: a review of *in vitro* activity, pharmacokinetics, pharmacodynamics and clinical utility. *Clin. Microbiol. Infect.* 3, S87–S101
76 Namasivayam, S.K.R. (2017) Nanoformulation of antibacterial antibiotics cefpirome with biocompatible polymeric nanoparticles and evaluation for the improved antibacterial activity and nontarget toxicity studies. *Asian J. Pharm.* 11, 269–281
77 Ribeiro, L.N. *et al.* (2017) Natural lipids-based NLC containing lidocaine: from pre-formulation to *in vivo* studies. *Eur. J. Pharm. Sci.* 106, 102–112
78 Kumar, V. and Prud'Homme, R.K. (2008) Thermodynamic limits on drug loading in nanoparticle cores. *J. Pharm. Sci.* 97, 4904–4914
79 Wong, H.L. *et al.* (2004) Development of solid lipid nanoparticles containing ionically complexed chemotherapeutic drugs and chemosensitizers. *J. Pharm. Sci.* 93, 1993–2008
80 Madan, J. *et al.* (2013) Poly (ethylene)-glycol conjugated solid lipid nanoparticles of noscapine improve biological half-life, brain delivery and efficacy in glioblastoma cells. *Nanomedicine* 9, 492–503
81 He, H. *et al.* (2015) VB12-coated Gel-Core-SLN containing insulin: Another way to improve oral absorption. *Int. J. Pharm.* 493, 451–459
82 Severino, P. *et al.* (2015) Sodium alginate-cross-linked polymyxin B sulphate-loaded solid lipid nanoparticles: antibiotic resistance tests and HaCat and NIH/3T3 cell viability studies. *Colloids Surf. B Biointerfaces* 129, 191–197
83 Seedat, N. *et al.* (2016) Co-encapsulation of multi-lipids and polymers enhances the performance of vancomycin in lipid–polymer hybrid nanoparticles: *In vitro* and *in silico* studies. *Mater. Sci. Eng. C* 61, 616–630
84 Jain, S. *et al.* (2012) Gelatin coated hybrid lipid nanoparticles for oral delivery of amphotericin B. *Mol. Pharm.* 9, 2542–2553
85 Saito, T. *et al.* (2012) Possible factors involved in oral inactivity of meropenem, a carbapenem antibiotic. *Pharmacol. Pharm.* 3, 201
86 Mazumder, S.A. (2018) *Intravenous-to-Oral Switch Therapy*. MedScape
87 Lee, S. *et al.* (2012) Clinicians' knowledge, beliefs and acceptance of intravenous-to-oral antibiotic switching, Hospital Pulau Pinang. *Med. J. Malaysia* 67, 190–198
88 Craig, W.A. (1997) The pharmacology of meropenem, a new carbapenem antibiotic. *Clin. Infect. Dis.* 24 (Suppl. 2), S266–S275
89 Abdelkader, A. *et al.* (2017) Ultrahigh antibacterial efficacy of meropenem-loaded chitosan nanoparticles in a septic animal model. *Carbohydr. Polym.* 174, 1041–1050
90 Mhango, E.K. *et al.* (2017) Preparation and optimization of meropenem-loaded solid lipid nanoparticles: *in vitro* evaluation and molecular modeling. *AAPS PharmSciTech* 18, 2011–2025
91 Bobo, D. *et al.* (2016) Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. *Pharm. Res.* 33, 2373–2387
92 Caster, J.M. *et al.* (2017) Investigational nanomedicines in 2016: a review of nanotherapeutics currently undergoing clinical trials. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 9, e1416
93 Ventola, C.L. (2017) Progress in nanomedicine: approved and investigational nanodrugs. *Pharm. Ther.* 42, 742
94 Wolfram, J. *et al.* (2015) Safety of nanoparticles in medicine. *Curr. Drug Targets* 16, 1671–1681
95 Onoue, S. *et al.* (2014) Nanodrugs: pharmacokinetics and safety. *Int. J. Nanomed.* 9, 1025