



Innovative drug delivery systems for leprosy treatment

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Introduction

Leprosy is one of the oldest human epidemic diseases and is still endemic in some areas.^{1,2} The last WHO report, from 2018, counted 208,641 new cases globally, with India, Brazil and Indonesia concentrating approximately 80% (166,011) of them.² Dapsone, rifampicin and clofazimine constitute the multidrug therapy, which has reduced new leprosy cases remarkably, since its inception in the 1980s.³⁻⁵ According to the clinical type of disease, treatment duration varies from 6 to 12 months.⁶

Low adherence to therapy is one of the main hurdles for leprosy elimination as the disease requires prolonged treatment.⁷ A complex interplay of factors such as socioeconomic condition, inadequate healthcare service, and multidrug therapy underlie the poor adherence.⁷ Among the factors associated with multidrug therapy drugs, resistance and adverse effects are important.⁸⁻¹⁰ The first extensive study from endemic countries revealed that 8.0% of *M. leprae* strains underwent mutations, resulting in multidrug therapy resistance.⁹ However, a comprehensive study addressing drug adverse effects is still absent. Notably, a retrospective study from Brazil reported at least one adverse effect related to multidrug therapy in almost 37.9% patients.¹¹

An alternative treatment to WHO-multidrug therapy consists of rifampicin, ofloxacin and minocycline, called ROM. This alternate regimen utilizes the bactericidal/bacteriostatic activity of both drugs, ofloxacin and minocycline.¹² Although the resistance rate to ofloxacin (1.3%) is relevant, ROM-drugs usually present mild adverse effects.^{9,13}

Most drugs used for leprosy treatment have low water solubility, which limits their bioavailability.¹⁴⁻¹⁶ Accordingly, administration of high doses required for reaching therapeutic blood levels aggravate adverse effects. Poor water solubility of these drugs may also result in their variable serum concentration, thus increasing the likelihood of bacterial resistance.¹⁷⁻¹⁹ Additionally, rifampicin and clofazimine bioavailability may be limited, respectively, by stomach degradation and recrystallization depending on pH.^{11,20,21} Unlike other drugs, minocycline is highly water soluble, its major limitation being intestinal permeability.²²

New formulations have been proposed for leprosy therapy to address these problems. This article aims to highlight the recent advances in drug delivery systems, which may be utilized to overcome these hurdles.

Innovative pharmaceutical strategies towards enhancement of therapeutic efficacy

Recent advances in drug delivery systems may overcome solubility impairment, common in pharmaceutical development.²³ The oral formulations proposed for multidrug therapy drugs are focused on two main strategies: increasing the apparent drug water solubility or modifying the drug release.

Figure 1 summarizes the improvements and the expected results of multidrug therapy innovative formulations. *In vitro* evaluation, *in vivo*, and *in silico* performances of these preparations are provided in Table 1, if available, showing their potential therapeutic efficacy. As the following steps,

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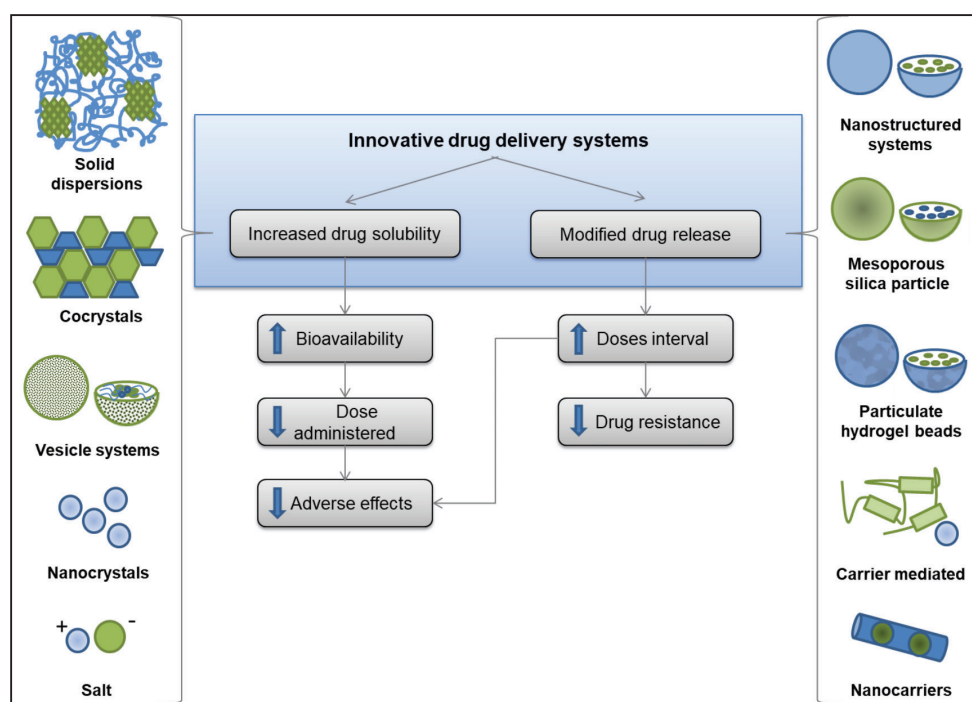


Figure 1: Innovative drug delivery systems formulations developed to overcome the main hurdles in the treatment of leprosy

well-established clinical tests will play a key role in ensuring their relevance for patients. Aiming to reach the market, a collaborative effort between government and private companies is essential.

Drug water solubility enhancement

For dapsone, innovative formulations obtained through synthesis of its chemical derivatives (salt and cocrystal) and solid dispersion were proposed to enhance water solubility.²⁴⁻²⁶ For example, solid dispersion increased water solubility by more than 7.5-fold, compared to free drug form.²⁴ The improved bioavailability may reduce the therapeutic dose.

The solubility of rifampicin has been improved by using nanocrystals, solid dispersion, vesicle systems (liposphere, niosome and liposome), and complex preparations.^{20,27-33} Rifampicin nanocrystals enable 2-fold increase of drug concentration in a formulation. This innovative preparation halves the original intended dose.²⁷ Apart from dose reduction, nanocrystals may increase permeation into intestine cells due to enhanced adherence.²⁷ Rifampicin absorption may be reduced to half by food, which may also be mitigated by nanocrystals.^{27,34}

Clofazimine innovative preparations include synthetic chemical derivatives (salt and complex) and nanotechnology-based delivery (nanoparticle and nanoporous silica particle).³⁵⁻³⁸ Amongst them, nanoporous silica particles increased its water solubility and intestinal permeability by 20-fold and 5-fold, respectively, compared to free-form.³⁷ These modifications can significantly reduce the effective therapeutic dose.

The formulations proposed to enhance ofloxacin solubility are cocrystal and cyclodextrin complex.^{39,40} Initially, such

formulations were developed for ophthalmic topical preparations. Minocycline does not present aqueous solubility issues,²² instead, newer strategies such as release modifications are aiming to improve its permeability.

Modified drug release

Modified release strategy aims to modulate drug release from the dosage form. For instance, enteric release is designed for intestinal drug delivery, protecting it from gastric pH. The extended-release formulations restrict drug delivery immediately following oral administration.^{29,30} The enteric release is especially relevant for rifampicin and clofazimine due to their chemical instability in acidic conditions.^{41,42}

Dapsone modified-release was proposed using different strategies such as polymeric nanoparticles, hydrogels and nanofibers.⁴³⁻⁴⁵ *In vivo* results of polymeric nanoparticles demonstrated the sustained co-delivery of dapsone and clofazimine could reduce their doses.⁴³ For rifampicin, strategies included nanoparticles (solid lipid, polymeric and lecithin), complex, and hydrogel beads.^{17,18,46,47} A formulation presenting an initial burst followed by sustained release is desirable, as observed in over 65% (4 of 6) (Table 1) of proposed rifampicin studies.⁴⁶⁻⁴⁹ Also, studies have shown favourable *in vivo* or *in silico* results. Among these, the increase in peak plasma concentration (C_{max}) is up to seven times higher than the free drug,^{17,18} using solid lipid nanoparticle strategy.¹⁷ Furthermore, rifampicin plasma concentration was sustained above the minimum inhibitory concentration (MIC) for five days, compared to two days of free drug (Table 1). Thus, these formulations can reduce the dose and minimize adverse effects.¹⁷

Table 1: Innovative pharmaceutical preparations for solubility/drug release improvement of leprosy drugs (dapsone, rifampicin, clofazimine, ofloxacin and minocycline)

DS	Innovative formulations	<i>In vitro</i> evaluation (Drug release/Solubility assessment)	<i>In vivo/in silico/in vitro</i> performance	Ref.
DAP	Solid dispersion (SD)	Drug release was nearly 1.9-fold compared to physical mixture and 7.5-fold compared to pure DAP (in first 10 min).	–	24
DAP and CFZ	Polymeric nanoparticles	Sustained release: after 24 h, 82% of DAP and 68% of CFZ.	NP was more effective than the same dose of the drugs.	43
DAP	Cocrystal	Best solubility achieved: 1.5 times, compared to pure DAP.	–	26
DAP	Hydrogel	In the first hours, up to 5%, after 4 h 10% and sustained release (up to 20%) in the next 22 h.	–	44
DAP	Nanofibers	After 400 min, 77.71%, compared to 80.61% of DAP nanoemulsion.	–	45
DAP	Salt and Eutectics	Dissolution rate of salt nearly 2-fold and eutectics 1.7-fold than pure DAP (in first 10 min).	–	25
RIF	Solid lipid nanoparticles (SLN)	Drug release was 70.12% after 9 days while free RIF was more than 90% in 24 h.	<i>In vivo</i> studies: C_{max} in plasma, SLN: 15.12 µg/ml, Free RIF: 2.27 µg/ml. Relative bioavailability was improved 8.16 times (compared to free RIF), with sustained levels for 5 days.	17
RIF	Particulate hydrogel beads	Constant and sustained drug level throughout 24 h, with highest amount of drug released of 71.49%.	–	49
RIF	Solid dispersion	Drug release was 82.3%, compared to 32.7% of RIF powder (at 60 min, pH 6.8).	–	28
RIF	Solid lipid nanoparticle (SLN)	85% within approximately 6 min at both pHs performed (1.2 and 6.8).	<i>In vivo-in silico</i> assessment: AUC and C_{max} increased by 3.72 and 5.22-fold compared to the RIF suspension. GastroPlus™ predicted maximum compartmental absorption from proximal and distal portions of the intestine.	18
RIF	Chitosan/gelatin/lecithin nanoparticles	Drug release was more than 3-fold up compared to free drug, at higher concentration of lecithin (2.0 g), in pH 7.2.	–	48
RIF	Carboxymethylcellulose complex	Drug release was $99 \pm 3\%$ at 15 min, compared to two commercial medicines of less than 80% and approximately 90%.	–	33
RIF	Phospholipid lipospheres	The best formulation presented solubility of 350.9 ± 23 µg/mL compared to 105.1 ± 12 µg/mL of pure drug.	Antimycobacterial activity enhanced compared to pure drug. Peak plasma concentration (C_{max}) was 109.92 ± 25 µg/mL compared to 54.31 ± 18 µg/mL of pure drug. The AUC was 406.92 ± 18 µg h/L compared to 147.72 ± 15 µg h/L of pure drug.	29
RIF	DIMEB complex	Improved solubility, at pH 7.4, achieving the equilibrium in approximately 9 h.	–	20
RIF	Solid lipid nanoparticles (SLN)	Biphasic profile: initial burst followed by sustained pattern (up to 90% drug in 120 h).	–	46
RIF	Niosome	Between 61.69% and 75.90%, compared to 32.43% of pure RIF (after the first 2 h).	–	30
RIF	Co-polymeric nanoparticles (NP)	Solubility improved 65-fold compared to pure drug. Controlled release achieving up to 70 h, compared to 6 h of pure drug.	–	47
RIF	Niosome	Achieving 80% of drug release compared to 40% of pure drug, over 12 h.	–	31
RIF	Liposomes	Drug release achieved 95% released after only 5 h, compared to nearly 70% of free drug.	–	32
RIF	Nanocrystals	Nanocrystals showed up to 1.74-fold on solubility compared to commercial product.	–	27
CFZ	Alginate-mediated carrier	The release rate decreases upon increasing alginate concentrations.	–	58
CFZ	Complex formation	Increased approximately 0.53-fold of the maximum solubility compared to CB[7].	The analysis of MIC50 between complex and free drug did not show significant statistical difference.	38

(Contd...)

Table 1: (Continued)

DS	Innovative formulations	<i>In vitro</i> evaluation (Drug release/Solubility assessment)	<i>In vivo/in silico/in vitro</i> performance	Ref.
CFZ	Nanoporous silica particles	Solubility was increased by 20-fold in simulated gastric fluid.	Permeation studies (using Caco-2 intestinal cells) showed more than 5-fold increased intestinal permeation in comparison to the free drug (below the detection limit).	37
CFZ	Enzyme-mediated carrier	Only CFZ binded to pepsin remains in solution in the intestinal environment (pH~5.4)	–	56
CFZ	Polymeric nanoparticle	Sustained pattern, about 30% at the end of the experiment (buffer solution - pH 6.8 for 8 h, at 37°C).	–	42
CFZ	Mesoporous silica particles (MPS)	At pH 4.1, maximum of 29% for ho-MSP (more hydrophobic) and 46% for hi-MSP. At pH 6.8: rapid release from hi-MSP, with 2 times higher initial release, compared to ho-MSP. However, both released nearly 10%.	–	57
CFZ	Nanoparticle (NP)	The NP, mainly in presence of fat, was faster dissolved compared to drug substance or to Lamprene®.	–	36
CFZ	Salt	Improvement of 5-fold on solubility compared to the free drug.	–	35
OFL	Cocrystal salt	After 1h, the amount of dissolved from cocrystal was more than 3-fold, compared to pure drug.	–	39
OFL	Inclusion complex	Solubility increased 3.7-fold compared to pure drug.	–	40
OFL	Nanoparticle cellulose conjugates	Nanoparticles showed sustained release proved in a pharmacokinetic study.	AUC was 1.6–2.3 times higher than controls rabbits.	59
OFL	Nanofibres	Initial rapid release (>50% of drug released within 4 h), followed by a slow and sustained release phase.	Enhanced <i>in vitro</i> antimicrobial activity, and <i>in vivo</i> mucoadhesion and gastro-retention in rats.	60
OFL	Polymeric complex	Release of 45–57% in 50 h.	Formulations demonstrated activity against <i>M. tuberculosis</i> in <i>in vitro</i> microbiological studies.	61
OFL	Nanoparticle (NP)	Maximum drug release of 76% observed after 18 h (ph 2.2).	Proven antibacterial activity against <i>E. coli</i> .	62
OFL	PEGylated nanoparticle (NP)	The best nanoparticles obtained released 96% of OFL in 36 h. Free drug was released 100% in less than 4 h.	Better bactericidal activity compared to free drug. And inhibition of <i>Bacillus subtilis</i> resistance.	63
MINO	Hydrogel	Initial burst release with subsequent release control, achieving 100% only after more than 48 h.	–	64
MINO	Nanoparticle	Drug release achieved nearly 90% only after more than 10h. Free drug achieve the same percentage within 1 h.	Antimicrobial activity was comparable to the free drug.	65
MINO	Solid lipid nanoparticle (SLN)	<i>In vitro</i> release was kept continuous during 7 days.	SLN was twice as efficient as free drug, in animal tests.	66
MINO	Polymeric nanoparticles	The NP presented an initial burst during 24h and a linear release over 30 days, compared to more than 98% within two days of free drug.	–	67

DS: Drug substance; Ref: References; DAP: Dapsone; RIF: Rifampicin; CFZ: Clofazimine; OFL: Ofloxacin; MINO: Minocycline; h: hours; AUC: Area under the curve; DIMEB: Heptakis(2,6-di-O-methyl)- β -cyclodextrin

Nano-based drug delivery systems have been approved by regulatory agencies and prescribed in the last decades, reinforcing their efficacy and safety.^{50,51} For instance, liposomal amphotericin B (AmBisome®) has been used to treat leishmaniasis successfully.⁵² Nevertheless, the particle size and shape can impact the nanoparticle distribution.⁵³ For example, nanorods may accumulate in organs related to immune response and blood clearance, such as lymph nodes, spleen, liver and bone marrow.⁵⁴ Consequently, risk assessment and quantification methods have been increasingly explored aiming to evaluate nanomedicine effects for patients.^{54,55}

Clofazimine, in turn, can recrystallize outside a pH range of 2–4, thereby compromising absorption.⁵⁶ Polymeric

nanoparticles, alginate, pepsin and mesoporous silica are examples of carriers developed to modify the release of clofazimine.^{37,42,56–58} Polymeric nanoparticles ensured sustained release and lower cellular toxicity in Caco-2 and HT29-MTX cells, compared to free drug. Thus, these studies corroborated the success of this strategy to avoid clofazimine recrystallization.⁴²

Strategies for ofloxacin included cellulose conjugate, nanofibers, polymeric complex and nanoparticles.^{59–63} *In vivo* studies using nanofibers depicted its role as ofloxacin reservoir, increasing its residence time in the gastrointestinal tract. Besides, an *in vitro* study showed significant mucoadhesion using a strip of rat's gastric mucosal membrane and improved efficacy against micro-organisms, such as *E. coli*, *E. faecalis*,

S. aureu, and *P. aeruginosa*. Therefore, these studies represent advanced formulations with a better oral absorption profile in leprosy treatment.⁶⁰

Formulations containing minocycline were mainly developed for topical application, focused on periodontal diseases. However, the modified release approach might be considered to overcome its permeability issue. Hydrogel, nanoparticles, solid lipid nanoparticles and polymeric nanoparticles have been proposed to achieve this goal.⁶⁴⁻⁶⁷

Conclusion

Leprosy elimination involves a series of treatment-related challenges, leading to poor patient adherence. The multidrug therapy drugs are distributed free of charge; however, their low water solubility, severe adverse effects and resistance potential limit treatment completion. Innovative drug delivery systems are being proposed to overcome these limitations, involving two main targets: water solubility improvement and sustained drug release. Enhanced solubility may reduce the administered dose to patient, thus minimizing adverse effects. A modified drug release approach may increase dose interval, reducing the occurrence of bacterial resistance and adverse effects. These modifications may improve patient adherence to treatment, diminishing bacillary spread by untreated patients. A reinvention of leprosy treatment may promote patient healing and interrupt transmission, two essential goals towards a leprosy-free world.

Declaration of patient consent

Patient's consent is not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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