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Praziquantel As The Gold Standard Of Schistosomiasis Control Drug Delivery And Nanotechnological Strategies

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Abstract – The poor rate of drug discovery for the control of Neglected tropical diseases (NTDs) including schistosomiasis has necessitated effective management of existing drugs by modulating their delivery. Nanotechnology-based colloidal drug carriers have been explored to improve the activity and safety profile of drugs for NTDs including parasitic diseases. In developing new drug delivery systems for schistosomiasis, research efforts have focused mainly on Praziquantel (PZQ) as the sole antischistosomal agent in current clinical practice. Carrier systems of the polymer, inorganic and lipid-based type have been investigated for the delivery of PZQ. However, promising results were obtained using lipid-based delivery systems including liposomes, solid lipid nanoparticles, nanostructured lipid carriers and nanoemulsions. Selection of these lipid carrier systems has been based on the lipophilicity of PZQ, controlled drug release, potential increase in its bioavailability by promoting lymphatic absorption to bypass the extensive first pass effect biodistribution to the host liver and enhancement of PZQ interaction with the worm tegument of a similar phospholipid nature.

Keywords – Nanotechnology, Praziquantel, Drug delivery systems, Schistosomiasis

I. INTRODUCTION

Praziquantel (PZQ) is the exclusive treatment to date for schistosomiasis [1]. The drug name's etymology is p(y)razi(ne) chemical component + qu(inoline) chemical component + ant(h)el(mintic) [2]. PZQ was discovered in the 1970s by Merck and Bayer [3]. It was revolutionary because it could be administered orally and had very few unwanted side effects. As a result of marked reductions in the price of PZQ, the rate at which it is used has accelerated greatly in recent years [4].

The benefits of PZQ reside in its high efficacy, ease of administration, relative safety, and price [5]. The efficacy of PZQ measured by parasite egg excretion about four weeks after treatment with 40 mg/kg can be very broadly summarized as 60–90% cure (no eggs in feces) and 80–95% average reduction in the number of excreted eggs in non-cured patients. However, 100% cure is seldom achieved and these figures are probably overestimated due to the relative insensitivity of diagnostic methods.

Praziquantel is administered orally in a standard dose of 40 mg/kg. The dose may be subcurative, but increasing the dose to 60 mg/kg does not seem to improve activity [6]. The safety of PZQ has been the subject of a massive amount of data collected over the years, with regard to both immediate and delayed effects. Overwhelming evidence indicated that PZQ may be considered the safest of all anthelmintic drugs. This was demonstrated for different geographical settings [7], different parasite species [8], and different patient ages and conditions [9]. Reversing previous practice, an informal WHO consultation concluded that pregnant and lactating women should also be treated, since the benefits of treatment clearly exceed hypothetical risks. Short-term adverse reactions do occur in a significant number of cases, but they are usually mild and of short duration [6]. These include nausea, dizziness, rash, pruritus, headache, drowsiness, and abdominal pain [5].

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The recommended dosage to treat schistosomiasis is 20 mg/kg three times in one day, and since PZQ does not act on juvenile worms, follow-up treatment 4 to 6 weeks later is strongly advised [10]. In preventive chemotherapy programs, PZQ is administered as a single 40-mg/kg dose to at-risk populations [11].

The detailed molecular mechanisms of PZQ actions are still poorly defined, though some effects on schistosome worm morphology and physiology are well-known. Experimental evidence indicates that praziquantel increases the permeability of the membranes of schistosome cells towards calcium ions by targeting the beta (b) subunits of voltage-gated calcium ions (Ca^{2+}) channels [12].Within seconds of exposure to the drug, adult schistosomes exhibit a rapid, sustained contraction of the worm's musculature [13], and vacuolization and disruption of the parasite tegument [14]. This effect is associated with the subsequent exposure of parasite antigens on the surface of the worm. Both of these responses are thought to be linked to a PZQ-dependent disruption of Ca^{2+} homeostasis [15]. Adult schistosomes are then swept back through the portal circulation to the liver, where they are destroyed by phagocytes. Figure (1) depicts the marked alterations in the schistosomal surface after PZQ exposure.

The other effects of praziquantel are often referred to as 'secondary' because they are considered to be related to, or a consequence of, the primary effects. Such phenomena include changes in carbohydrate, protein and nucleotide metabolism; decrease in enzymatic activities; and changes in the properties of surface membranes [16].

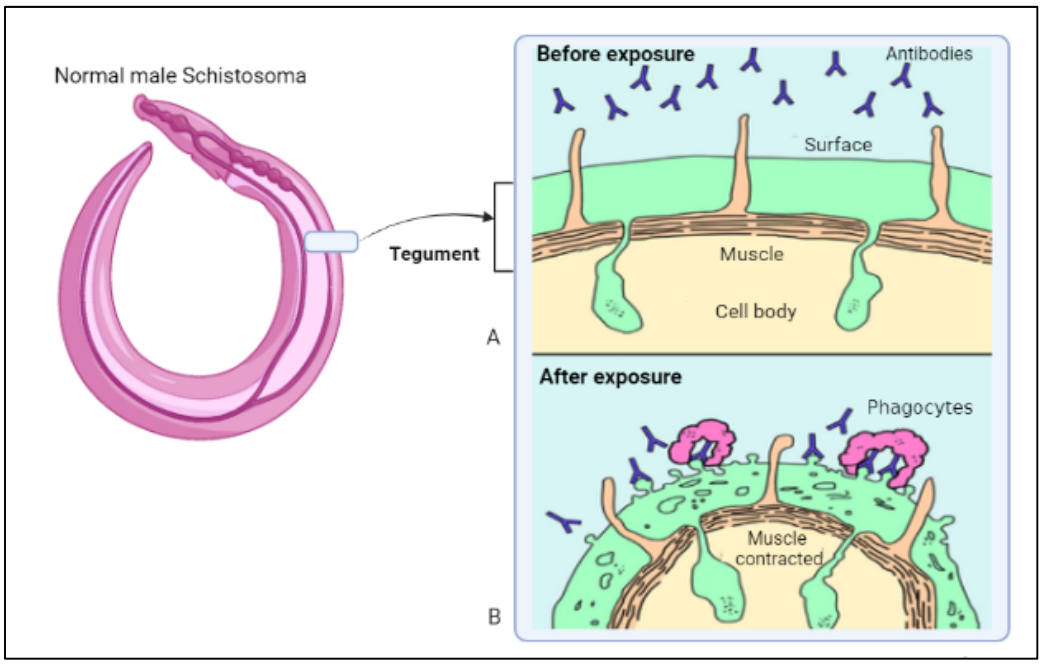

Figure 1: Possible mechanisms of parasite elimination following exposure to Praziquantel.

Before exposure to praziquantel, the schistosome is capable of avoiding antibodies directed toward surface and internally located antigens. A, Cross-section of the surface of a normal schistosome. After exposure to praziquantel, the muscles of the schistosome contract because of drug-induced influx of Ca^{++}. B, Changes in the schistosome tegument include small holes and balloon-like structures and exposure of hidden parasite antigens, resulting in the binding of antibodies and phagocytes [17].

Praziquantel is rapidly and well absorbed (80%) following oral administration with a t_{max} of approximately 1−3 h Figure (2). Measurable amounts appear in the blood as early as 15 min after dosing [18]. Maximum plasma concentration after a standard dose of 40 mg/kg shows wide inter-individual variations in the range of 200 to 2,000 ng/ml [19]. The dissolution of PZQ in fed simulated intestinal fluid (FeSSIF) is faster than fasting simulated intestinal fluid (FaSSIF) [20]. The C_{max} and AUC of PZQ were reported to be higher relative to the fasting state when administered with food, although the variability is also increased [21]. PZQ should always be taken with food.

PZQ undergoes significant first-pass metabolism through the liver enzyme cytochrome P450 (CYP) 3A4 and to a lesser extent through 1A2 and 2C19 ([22], [23]). Hence, large doses are required to achieve adequate PZQ concentration at the target sites [24]. (R)PZQ is metabolized at a much higher rate than (S) PZQ. (R) PZQ is transformed mainly into *cis*- and *trans*-hydroxypraziquantel (4-

OH-PZQ), while (S) PZQ is converted to other monohydroxylated metabolites. In humans, the main metabolite is trans-4-OH-PZQ [25]. The first pass effect is associated with rapid disappearance of PZQ from the circulation ($t_{1/2}$ranges between 1 and 3 h). PZQ and its metabolites are mainly excreted in the urine. Elimination is more than 80% complete after 24 h [26].The most abundant metabolite in urine is the 4-hydroxy-cyclohexylcarbonyl analog which represents about two thirds of total urinary metabolites [27].

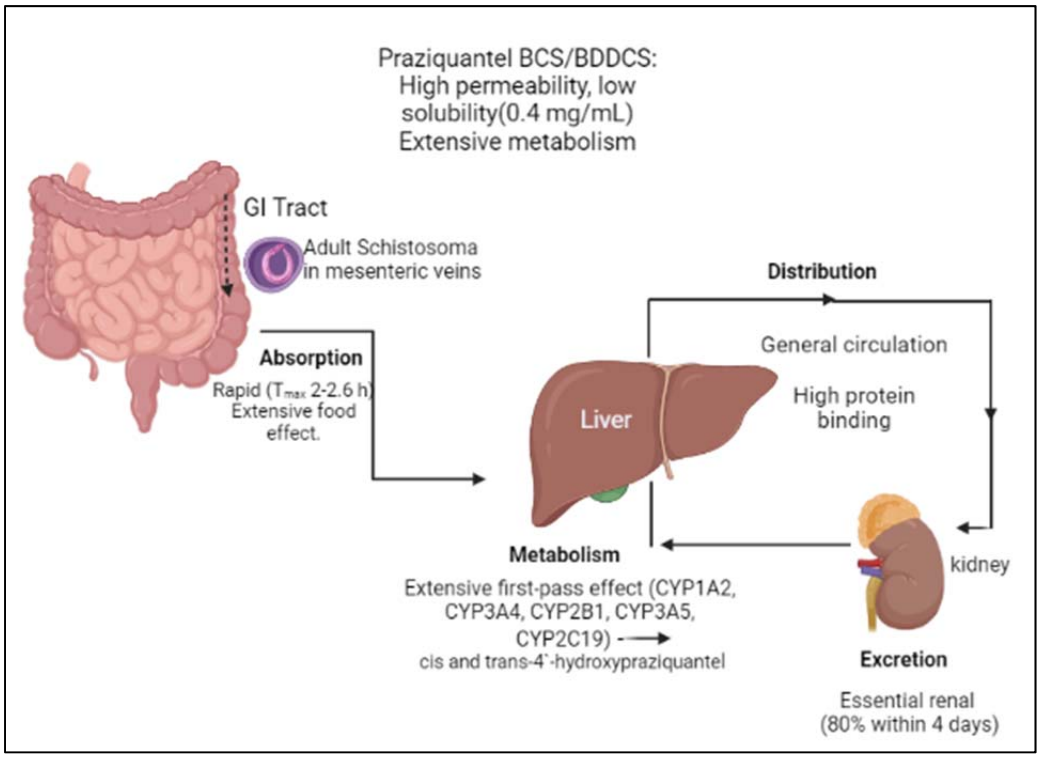

Figure 2: Schematic diagram showing the principal characteristics of praziquantel absorption, distribution, metabolism and excretion ('ADME'). GI, gastrointestinal [28].

II. Limitations of Praziquantel in the Control of Schistosomiasis

While the efficacy against all schistosoma species and the safety are outstanding, PZQ has several drawbacks regarding administration, PKs and clinical effectiveness. The major drawbacks involving administration include the large dose needed, 40 mg PZQ/kg bodyweight and the bitter and disgusting taste caused by the inactive (S) enantiomer. These can lead to gagging or vomiting if tablets are chewed contrary to recommendation [29]. The resulting poor compliance may lead to untreated and uncured cases. Such administration problems are particularly of concern to children. Dosages in children are determined by measurement of children's heights using tablet poles, and range from one to five 600 mg tablets for one treatment. Especially young children have been reported not to be able to swallow these 600 mg tablets [30]. Traditional methods of taste-masking, like the addition of aromas or sugar, are ineffective for PZQ.

A main pharmacokinetic limitation of PZQ therapy is the poor PZQ bioavailability due to the first pass effect and the short plasma half-life (0.8–1.5 h) ([30, [31]). Hepatic metabolism and inactivity of the (S) enantiomer both necessitate administration of a large dose of the drug to achieve sufficient plasma concentrations of PZQ at the larval tissues for eradication of cestode infection [32].

As to the clinical effectiveness, PZQ treatment lacks efficacy against juvenile schistosomes. This has been clearly shown in *in vitro* tests [33] and confirmed by clinical data [34]. The sensitivity of schistosomes to PZQ has a peculiar biphasic profile, with the earliest stages (from cercariae to the first few days after infection) being susceptible, followed by progressive insensitivity down to very low levels around 3 to 4 weeks after infection [34]. The best results are achieved during the 5th and 6th weeks post infection [35]. This parasite age-dependence of PZQ activity means neither can early infection be treated nor reinfection be prevented [36], a factor contributing to most treatment failures experienced in clinical practice [27].

Further, development of PZQ resistance is a major increasing concern since the drug has been in use for more than 30 years. Loss of PZQ efficacy would set back helminth control efforts. Epidemiological evidence reveals the emergence of PZQ-resistant/tolerant schistosomes [37]. Resistance is defined as a genetically transmitted loss of sensitivity in a parasite population that was previously sensitive to a given drug [38]. Tolerance is an innate insusceptibility of a parasite to a drug, with the caveat that the parasite must not have been previously exposed to the drug [38]. The first reports of possible PZQ resistance came from Senegal and Egypt respectively [39]. Drug treatment results in the emergence of schistosome resistance to PZQ as it removes drug-susceptible parasites in infected human beings, with the survival of resistant parasites [40]. It also may result in increased expression of the P-gp efflux pump, which is often involved in drug resistance mechanisms[41]. Once the proportion of human with drug-resistant strain produced by drug treatment is larger, the number of human and snails with resistant strain increases [42].

Such limitations of PZQ chemotherapy and the risk of relying on a single drug are urging the search for alternative effective and safe therapeutic and preventive approaches for the control of schistosomiasis.

III. ALTERNATIVE APPROACHES FOR EFFECTIVE CONTROL OF SCHISTOSOMIASIS

Despite the acute need for new drugs to replace PZQ, discovery and development of alternative antischistosomal drugs from lead drug candidates is hurdled by high cost amounting to hundreds of millions of dollars and the need for technology-rich laboratories and clinics. The process is also risky, in that as few as 5% of candidate drugs that enter clinical trials achieve approval and clinical use [43]. Importantly, profit incentives to drive innovation for the poor, the main victims of NTDs, are usually lacking [44]. Of the 850 new therapeutic products approved between 2000 and 2011, only 4% were indicated for neglected diseases, even though these diseases account for 11% of the global disease burden [45]. Therefore, apart from attempts to discover new antischistosomal agents, different alternative approaches have been considered for effective chemotherapy and chemoprophylaxis of schistosomiasis till backup compound for PZQ of comparable efficacy and breadth of application is available.

1- Discovery of new antischistosomal agents

Despite the high cost and risk of new drug discovery, novel schistosomicidal agents have been investigated mainly by the screening of random compound libraries directly on the parasite maintained in culture. Examples include oxadiazoles [46], substituted pyrimidinedione derivatives [47], hexadecyloxypropyl (HDP) cyclic-(S)-HPMPA and HDP-cyclic-cidofovir [48] and imidazolidines [49]. Promising results have been obtained *in vitro* or in preclinical animal studies, though no other drug than PZQ hit the markets to date.

2- Enantioselective synthesis of the active (R)-(-) praziquantel

Praziquantel is administered as a racemate, the schistosomicidal activity arising from the (R) enantiomer only, whereas the inactive (S) enantiomer contributes to the large dose and bitter taste of PZQ (Figure 3). The straightforward and low-cost chemical synthesis is assumed as the reason for the use of the racemate.

The WHO's Special Programme for Research and Training in Tropical Diseases (TDR) has assigned the low-cost preparation of pure schistosomicidal (R)-PZQ a key priority for future R&D on PZQ. Enantioselective synthesis of the active (R)-(-) PZQ has been the subject of chemical research and patent applications ([50], [51]) in order to reduce the PZQ dose and bitter taste [52].

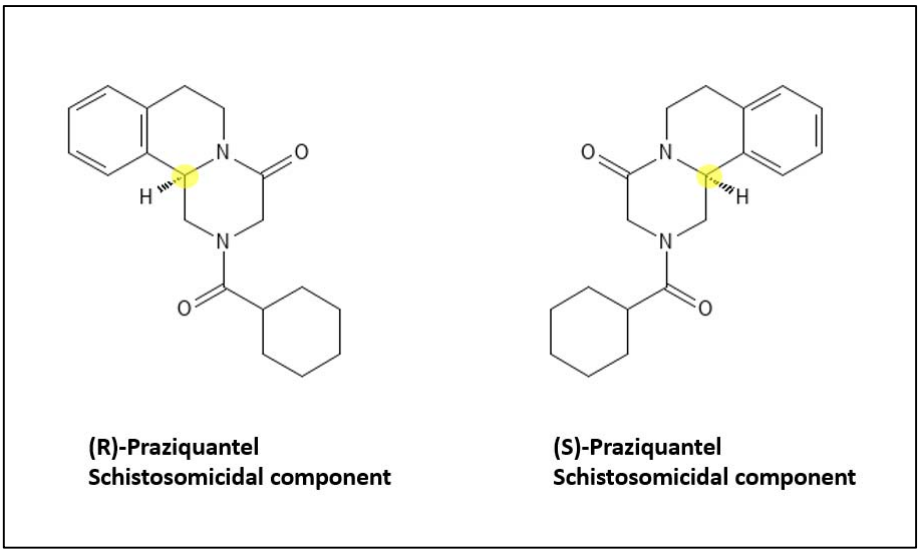

Figure 3: Molecular structures of the two mirror-image componentsof PZQ; asymmetric carbon atom highlighted in yellow[52].

3- Discovery of new schistosome therapeutic targets

The recent publication of the genome sequences of a variety of parasites including the three main species of schistosomes that infect humans ([53], [54]) means that approaches targeting specific gene products or pathways can be envisaged. These can include enzymes with activities specific to the parasite, or at least not found in the human host [46], metabolic bottlenecks, or molecules that are targeted in other pathologies.

Further, knowledge of the epigenetic mechanisms, which play a crucial role in the

schistosome development and differentiation rendered these mechanisms viable drug targets [55]. These include DNA methylation, reversible post-translational modifications of histones, histone variants, chromatin remodeling factors and non-coding RNAs. Indeed, two histone deacetylase (HDAC) inhibitors have already been approved for use and a number of other candidate drugs are undergoing clinical trials [56].

The antiarthritic gold drugs such as auranofin, aurothiomalate, and aurothioglucose, among several others compounds, were evaluated as potential inhibitors of the parasite enzyme thioredoxin glutathione reductase (TGR) based on the premise that *Schistosoma mansoni* TGR is an essential parasite enzyme. Gold complexes were found to be potent Schistosome TGR inhibitors [57]. Moreover, large libraries of compounds that affect epigenetic factors are available for testing against parasites [56].

This type of approach also has the advantage that the molecular mechanism of action of a given compound, which is required for any new drug, is much easier to determine than with the random screening approach [58].

4- Antischistosomal natural products and natural product-derived compounds

There is renewed global interest in natural products (NPs)as a starting point for drug discovery and development for schistosomiasis [59]. A prominent example of a semi-synthetic natural product derivative used against NTDs is ivermectin. The drug is considered an enigmatic multifaceted ‘wonder’ molecule that continues to surprise and exceed expectations [60]. Some of the other most interesting antischistosomal compounds are derivatives of artemisinin, such as artemether and artesunate ([61], [62]).

A plethora of plant extracts and oils of several medicinal plants were tested for potential therapeutic activity against schistosome infection [63], and were exhaustively compiled in excellent reviews ([56] , [64], [65]). The most successful product was myrrh, an oleo-gum resin extracted from the stem of Commiphora molmol, believed to affect schistosome musculature, leading to uncoupling of male and female couples and their extravasation to the liver [66]. The product has been licensed for human use in Egypt in the form of gelatin capsules. However, conflicting reports on its efficacy shed doubts upon its usefulness as a novel therapy for schistosomiasis [67].

Furthermore, arachidonic acid, an omega-6 fatty acid, shown to exert antischistosomal activity [68] proved to be as efficacious as PZQ in treatment of schoolchildren [69].

Discovery of natural products andnatural product-derived compounds continues to contribute to accelerating the development of new schistosomidal leads, especially through the identification of unexplored, biologically active chemical scaffolds and structural optimization of natural products with previously established activity.

5- Antischistosomal metal nanoparticles

Selenium nanoparticles exhibit high bioavailability and antioxidant properties. Injection of these nanoparticles into schistosome-infected mice resulted in amelioration of the hepatic histopathology and decreased the granulomas diameters [70]. Moreover, the treatment significantly increased the level of glutathione and decreased the levels of nitrite/nitrate and malondialdahyde.

Gold nanoparticles (AuNPs) were demonstrated to exert an antioxidant and hepatoprotective against murine hepatic schistosomiasis [71]. Inoculation of mice with 100 µL AuNPs at different doses (0.25, 0.5, and 1 mg/kg mice body weight) twice on day 46 and day 49 postinfection reduced the total worm burden, the egg load in the liver and the granuloma size. AuNPs also decreased the activities of malondialdehyde and nitric oxide significantly, and increased the level of glutathione compared to the infected untreated group. Histopathological and biochemical data suggest that AuNPs could ameliorate infection-induced damage in the livers of mice. Further studies are needed to confirm the role of nanogold as an anti-schistosomal agent and its mechanism of action [72].

6- Drug repurposing for schistosomiasis control

Repurposing, also termed re-profiling, re-tasking, therapeutic switching or drug repositioning is the strategy of testing drugs that have been originally designed, evaluated and approved for human use but for a non-related disease ([73], [74]). Since the compounds have already passed clinical trials with full toxicological and pharmacokinetic profiles accelerated development timelines and lower risks are encountered with significant cost saving. As such, repositioning may circumvent the marginal financial return for drugs related to diseases afflicting the poor and offer a better risk-versus-reward trade-off compared with other drug development strategies.

Although different drug classes were considered for repurposing for the treatment of schistosomiasis, anticancer drugs exerted promising effects [75]. Indeed, parasites and cancer bear similarities in basic biological characteristics being composed of populations not subjected to regular signaling mechanisms and able to make use of signals and resources for survival ([76], [77]).

In earlier studies, miltefosine (MFS), an alkylphosphocholine agent used for the local treatment of cutaneous metastases of breast cancer and oral therapy of visceral leishmaniasis, was tested for the treatment of *S. mansoni*. *In vitro* and preclinical data in mice demonstrated that MFS exerts significant activity against different developmental stages of *S. mansoni* upon oral administration in 5 consecutive daily 20 mg/kg doses ([78], [79]). Edelfosine, another alkylphosphocholine was also reported to exert antischistosomal activity [80].

7- Drug delivery and nanotechnological strategies

The poor rate of drug discovery for the control of NTDs including schistosomiasis has necessitated effective management of existing drugs by modulating their delivery. Nanotechnology-based colloidal drug carriers like emulsions, liposomes and nanoparticles have been explored to improve the activity and safety profile of drugs for NTDs including parasitic diseases ([81], [82], [83]). As a platform for the modern parasitic chemotherapy, these nanocarriers should target the drug specifically to the parasite to the maximum possible extent in order to minimize the adverse effects arising during the treatment.

Accordingly, the design of nanopharmaceuticals for NTDs should be based on a thorough knowledge of the pathophysiology of the disease, the peculiarities of individual infectious agents, the drug, the delivery system and interactions thereof ([82], [84], [85]). Information should also be available on the different types of therapeutic targets and the biological barriers to be overcome in order to reach them effectively and with the least harm to the patient [86].

Regarding the causative agent, complete information about its life cycle, interaction with the host and localization within the host organ, tissue or cells during the acute and chronic phase of the disease must be available.

Another crucial factor in the design of effective drug delivery systems encompasses the physicochemical and biopharmaceutical properties of the drug, particularly its solubility/permeability, in addition to its pharmacokinetic/pharmacodynamic (PK/PD) relationship. The delivery system should be selected to maximize drug access of therapeutic targets by modulating the drug physicochemical properties and its molecular (PK/PD) relationship. In other words, improving biospecificity (targetablity) rather than bioavailability may be the sole objective behind the design of drug delivery system ([87], [88], [89], [90]). In addition, enhancement of patient compliance in mass chemotherapy in terms of the route and frequency of administration, dose size and palatability of oral delivery systems, is of great importance for achieving the predetermined therapeutic outcomes.

In developing new drug delivery systems for schistosomiasis, research efforts have focused mainly on PZQ as the sole antischistosomal agent in current clinical practice. Carrier systems of the polymer [91], inorganic [92] and lipid-based type ([93], [94]) have been investigated for the delivery of PZQ. However, promising results were obtained using lipid-based delivery systems including liposomes, solid lipid nanoparticles, nanostructured lipid carriers and nanoemulsions. Selection of these lipid carrier systems has been based on the lipophilicity of PZQ, controlled drug release, potential increase in its bioavailability by promoting lymphatic absorption to bypass the extensive first pass effect [32] biodistribution to the host liver [95] and enhancement of PZQ interaction with the worm tegument of a similar phospholipid nature [35]. As such, the dose and side effects of PZQ could be reduced.

A. Lipid-based praziquantel drug delivery systems

1-Liposomes

Among various lipid-based carriers, liposomes as phospholipid vesicles were the earliest and most widely investigated delivery system for PZQ to modify its PKs and antischistosomal activity. For instance, PZQ encapsulation in liposomes was shown to retain PZQ in the liver of mice ten days after administration oral [95]. Orally administered liposomes were also demonstrated to improve the antischistosomal activity of PZQ as indicated by the decrease in the amounts of eggs and parasites [96]. Later on, Frezza et al., [35] reported a similar increase in PZQ activity following oral administration of increasing doses of liposomal PZQ to mice compared to untreated controls. This was manifested as a reduction in worm load, the number of eggs in the intestine and the number of hepatic granulomas. Results have been attributed to improved bioavailability in the host organism and better absorption of PZQ by the tegument of *S. mansoni*, which has an affinity for phospholipids.

2-Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) are surfactant-stabilized colloidal lipid suspensions or submicron sized aqueous dispersions of solid lipids produced by replacing the liquid lipid (oil) of an o/w emulsion by a solid lipid or a blend of solid lipids, i.e. the lipid particle matrix being solid at both room and body temperature ([97], [98]). They combine advantages of various traditional carriers. Identical to polymeric nanoparticles, SLN possess a solid matrix, protective for chemically labile actives and giving the ability to modulate drug release. Identical to nanoemulsions and liposomes they are composed of well-tolerated, regulatorily accepted lipids and can be produced easily on a large industrial scale [99]. SLN are a promising drug delivery system for oral administration of poorly water soluble drugs because of their capacity to increase the solubility of drug molecules when loaded in their lipid matrices, improving bioavailability [100].

PZQ loaded SLN exhibited a relatively long-term physical stability after storage at 4^{o}C, without drug expulsion [101]. Further, incorporation of PZQ in SLN was demonstrated to significantly enhance the drug bioavailability in rats compared to PZQ tablets [94]. Mishra et al. [32], attributed the increase in bioavailability of PZQ-SLN to intestinal lymphatic delivery based on intraduodenal administration to rats in the presence and absence of cycloheximide, a blocker of the intestinal lymphaticpathway. Further, a hydrogenated castor oil SLN suspension significantly enhanced the pharmacological activity and therapeutic efficacy of PZQ [102]. Combined data indicate that SLN are promising to enhance PZQ bioavailability and activity.

3-Nanostructured lipid carriers

Nanostructured lipid carriers (NLC), the second generation of SLN, are composed of a solid lipid matrix with a certain content of a liquid lipid (oils). To obtain the blends for the nanocarrier matrix, solid lipids are mixed with liquid lipids, preferably in a ratio of 70:30 up to a ratio of 99.9:0.1 ([103], [104]). NLC easily incorporate lipophilic drugs allowing for improved physical

stability of the system compared to SLN [105]. There are three types of NLC depending on their lipid composition and oil content : (i) the imperfect type, (ii) the multiple type, and (iii) the amorphous type which could affect drug loading [106].

Intestinal absorption of PZQ incorporated into NLC using the everted gut sac model indicated dependence of absorption rate on the matrix rigidity ([107], [108]). The encapsulation of PZQ in NLC was reported to improvethe safety profile *in vitro* and to enhance the antischistosomal activity of PZQin the *S. mansoni* BH strain [107].

4-Nanoemulsions

Nanoemulsions (LNE) are fine o/w dispersions, having droplets covering the size range between 50 and 200 nm. They were introduced during the 50ies for the purpose of parenteral nutrition and are also referred to as mini-emulsions, fine-dispersed emulsions or submicron emulsions [109]. The lipid phase (10%–20% of the emulsion) could be fatty vegetable oils (e.g. soy oil) or middle chain triacylglycerols. Other ingredients such as phospholipids (stabilizers, 0.6%-1.5%) and glycerol (osmolarity regulation, 2.25%) could be added [110]. During recent years, LNE have been used as drug carriers for mainly lipophilic drugs and several formulations are nowadays commercialized like etomidate (Etomidat-Lipuro®) and diazepam (Diazepam- Lipuro®).

An oil-in-water (O/W) nanoemulsion(NE)-based platform for the delivery of PZQ in liquid form greatly enhanced the transport of PZQ across confluent and polarized Caco-2 cell monolayers when compared to free PZQ [111]. In a recent study, sustained-release thermosensitive PZQ-loaded nanoemulsion (PZQ-NE) hydrogel was shown to significantly improve the bioavailability of PZQ and slow down elimination, prolongingits mean residence time [112].

5- lipid nanocapsules

Lipid nanocapsules (LNCs), relatively new biomimetic nanocarriers [113], appear to integrate many of the prerequisites for nanocarrier-mediated oral drug delivery. They consist of a lipid core stealth-coated nanostructure with a relatively rigid phospholipid/ethoxylated surfactant shell, prepared using a low energy phase-inversion temperature method and approved ingredients. LNCs are characterized by a size range of 20–100 nm, structural stability in simulated gastrointestinal (GI) media ([114], [115]), and ability to diffuse in intestinal mucus [116].

LNCs with modified composition proved highly effective as oral nanovectors for a large dose drug, PZQ. a single 250 mg/kg oral dose of PZQ–LNCs significantly enhanced PZQ antischistosomal activity in S. mansoni-infected mice. PD activity combined with PK data and SEM imaging provided evidence for increased PZQ bioavailability in addition to intestinal translocation of PZQ–LNCs to target adult worms, a process promoted by the GI stability of LNCs. The study outcomes suggest LNCs as nanocarriers for improving the efficacy of orally administered drugs via systemic exposure enhancement and the oral targeting of therapeutically relevant distal sites [117].

B -Polymer-based praziquantel drug delivery systems

PZQ has been formulated as polymer-based nanoparticles using mainly PLGA and poly(methylmethacrylate) (PMMA) polymers [118]. In a series of articles, Minardes et al., prepared and characterized PZQ-PLGA nanoparticles ([119], [120]) and assessed the intestinal absorption of PZQ using the everted sac model[91]. Results indicated that PZQ encapsulation in PLGA nanoparticles resulted in reduced the drug absorption. The authors made the speculation that this nanoparticulate system can behave as a drug reservoir and/or to have a more localized effect in intestinal membrane for a prolonged period of time This would potentially allow PZQ to act on the parasites usually found in the mesenteric veins.

PZQ was also formulated as poly(methylmethacrylate) (PMMA) nanoparticles prepared by *in situ* miniemulsion polymerizations and intended for oral formulations to mask PZQ bitter taste [121]. Evaluation of the pharmacokinetic (PK) profile of PZQ-PMMA NP in Wistar rats indicated a reduction in PZQ bioavailability compared to free drug.

Accordingly, results obtained with polymer-based nanoparticles so far indicate that these systems did not enhance PZQ bioavailability pointing to the need for further studies to understand the PZQ-NP absorption mechanisms and the drug diffusion process through the polymer matrix *in vivo*.

C-Other praziquantel drug delivery system

Montmorillonite (MMT) clay was used as a delivery carrier of PZQ to overcome its known bioavailability drawbacks [92]. The PZQ-MMT clay nanoformulation provided a preparation with a controlled release rate and decreased crystallinity.

Investigation of the oral bioavailability of the nanoformulation and its *in vivo* efficacy against *S. mansoni* indicated improved bioavailability that was associated with higher efficacy. The dose necessary to kill 50% of the worms was reduced by >3-fold, with significant reduction in total tissue egg load and increase in total immature, mature, and dead eggs in most of the drug-treated groups. This formulation showed better bioavailability, enhanced antischistosomal efficacy, and a safer profile compared to free PZQ.

IV. Conclusion

Schistosomiasis (or Bilharzia) ranks second only to malaria in terms of human suffering in the tropics and subtropics. The aim of antischistosomal chemotherapy is two-fold, to cure the disease or at least minimize morbidity and to control transmission of the parasite in the endemic areas. The development of the broad-spectrum and relatively safe anti-helminthes drug, praziquantel (PZQ), resulted in a change of the global strategy from a multi-pronged transmission control approach to drug-based morbidity control, achieving a significant advance in the control of schistosomiasis. While the efficacy against all schistosoma species and the safety are outstanding, PZQ has several drawbacks regarding administration, PKs and clinical effectiveness. Such limitations of PZQ chemotherapy and the risk of relying on a single drug are urging the search for alternative effective and safe therapeutic and preventive approaches for the control of schistosomiasis. drug delivery technology and pharmaceutical nanotechnology have become popular terms representing the main efforts of the current science and technology to engineer delivery systems including nanomedicines to get drugs to their targets in a controlled manner. The development of new delivery systems is intended to enhance the therapeutic potency of Praziquantel by improving its absorption, distribution, metabolism and excretion (ADME), reducing its toxicity. Several types of nanocarriers have been exploited for the development of PZQ. These nanocarrier systems have shown promising results in the treatment of Schistosomiasis with diminished toxicity and increased efficacy as well as a prolonged release with a reduced number of dosages.

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