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Mini Review

The Possibility of Hot Melt Extruded Decoquinate Becoming the Next Orally Dosing Drug Targeting the Liver Stage of Malaria

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ABSTRACT

Decoquinate (DQ) is a water-insoluble agent with multistage antimalarial activity. A recent report has been published that describes how the Hot Melt Extrusion (HME) approach is applied to prepare solid dispersions of DQ, an Active Pharmaceutical Ingredient (API), to improve oral bioavailability. Instead of using organic solvents to make the dispersion of DQ in polymers, DQ was melt dispersed in polymer excipients at high temperatures without alteration of the structures of all ingredients. It is impossible to suspend DQ in water or an aqueous solution prior to the conversion of DQ to amorphous solid dispersion or solid solution. However, DQ dispersion prepared by HME becomes nanosized particles readily suspended in an aqueous solution, suggesting that drug particles in such dispersion can become available in the digestive tract and accessible to the intestinal surface for absorption. It is hoped that the DQ prepared by HME can be further developed into tablet formulations. The idea is to make tablet medication available for populations in an endemic area or travelers to the area to prevent *Plasmodium* (P) infection or treat malaria at the early stage (liver stage) so that they can be free of symptoms caused by blood-stage infection. But will this idea work? This brief review may help us know more about DQ.

Keywords: Decoquinate; Hot melt extrusion; Oral bioavailability; Liver stage malaria

INTRODUCTION

Earlier studies by others found that DQ had low nanomolar (2.6 nm) activity against *in vitro* liver stage *Plasmodium* parasites, about 3000-fold lower than that of primaquine [1-3] and a single 5 mg/kg oral dose completely protected mice against *Plasmodium* infection caused by mosquito bite [3]. Interestingly, among all compounds assessed, DQ had the highest therapeutic index (>2500) for treating *P. falciparum* 3D7 strain [2]. DQ is a cytochrome bc1 inhibitor with little cross-resistance against a panel of 5 strains of P. *falciparum* parasites resistant to the antimalarial drug atovaquone, another cytochrome bc1 inhibitor [2]. These important findings are scientific bases for developing this molecule as a useful antimalarial drug. Since then, however, work has been seldomly followed up to advance this drug development. The most likely reason is that without modification or formulation to improve the solubility, pure DQ is extremely difficult to use in *in vivo* studies.

Wang, et al. took the approach of formulation and particle size reduction to improve the bioavailability and antimalarial efficacy of DQ [4,5]. Compared to DQ microparticle suspension, a nanoparticle formulation of DQ orally dosed to mice had significantly increased DQ blood concentration (14.47-fold) and liver distribution (4.53-fold) and dramatically improved antimalarial efficacy (15-fold). Nanoparticle suspensions at a low oral dose of DQ completely protected mice from infection of *P. berghei* at the liver stage. A critical conclusion could be drawn from these studies that only small enough particles were made could DQ be effectively administered by an oral route and bioavailable. However, DQ nanoparticles were obtained, in addition to co-solvency and spray drying, by taking extra procedures such as ultrasonication or High-Pressure Homogenization (HPH) to bring down the particle size. To manipulate drug particles, DQ needs to be in a suitable physical form first. To achieve this, a large volume of organic solvents, usually with heating, is needed to dissolve DQ and then polymers

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and surfactants are added to the solution and mixed with DQ. The solvents are then removed by evaporation to bring all components together, which takes one or two days. At this point, a poorly soluble molecule DQ dispersed in drug carriers can then be suspended in the aqueous solution, which is a physical form for particle size manipulation. To get small enough particles, mechanic methods such as ultrasonication or HPH are essential, and the operation usually takes about two to six hours, sometimes even longer. Samples are then lyophilized and rehydrated for characterization and *in vitro* and *in vivo* evaluation. The lyophilization process is also time-consuming, a minimal 2 to 3 days due to a large aqueous volume. Back then, without being aware that HME was already available, it was the only way to obtain solid dispersion with nanosized particles. It was a long and complex process. Now we know that all these multi-step procedures from dissolving formulation ingredients in organic solvents to lyophilization of nanoparticles can be completed in one step via HME.

LITERATURE REVIEW

DQ: Suitable for making HME formulation

Wang, et al. [1] began to think of using HME to simplify the formulation procedures and to make the preparation more efficient after attending one of the seminars held in Shenzhen, China where Thermo Fisher scientific and Badische Anilin und Soda Fabrik (BASF) had the introduction and promotion of their HME-associated products. Although there had been excellent examples of making poorly water-soluble compounds into clinical drugs [6,7], no one knew if HME would work for DQ. Thus, a test of a few DQ formulations was run on HME through manufacturing suppliers before the machine was purchased. In the initial experiments, the output extrudates were examined and all formulations had mean particle size in micrometers [8]. Nevertheless, the project was moved forward. As more efforts had been made by young scientists in Wang's lab to adjust the processing parameters and the ratios of each formulation component, the quality of the output product was getting better and better. After the extruded solids were directly suspended in water or buffer with magnetic stirring for 24 hours and particle size was measured without any further particle size reduction, the mean particle size was comparable to the size of DQ nanoparticles prepared by the non-HME method [5]. Evidently, nanoparticles (below 250 nm) derived from the hot melt extrudate are formed through the HME process. Therefore, they are the nature of DQ HME formulation. Stirring in the buffer for 24 hours did not help reduce drug particle size and was only to ensure the solids were well suspended. DQ solid dispersion with nanosized particles used as oral dosage form in animal studies were shown to have sufficient bioavailability and prophylactic efficacy of the API. The formation of nanoparticles in the solid dispersion could be attributed to the selection of polymers (good miscibility of polymer/drug), the hot melt extrusion processing, and the processing parameters (appropriate melting temperatures and screw speed).

The ratio of drug to drug-loaded nanoparticles is one of the key criteria in evaluating the extrudate quality. Buffer or solution with with different pH, depending on the drug carriers, was chosen to suspend the DQ prepared by HME to observe physicochemical properties such as homogeneousness and drug load. Samples were stirred for 24 hours and fully mixed. The aqueous suspension of optimized formulations was homogeneous and remained to be stable for at least one week without particle size change, precipitation, agglomeration, and cloudiness. The amount of DQ suspended in an aqueous solution determined was greater than 90% of the total DQ added in selected formulations. The high content of DQ in aqueous suspension suggested that a high percentage of the drug had been incorporated into excipients and loaded in the drug particles. In other words, it was impossible for non-incorporated DQ to be present in the aqueous phase and therefore all detectable DQ was incorporated into the drug particles. Nano-sized particles present in the form of drug/excipient complex were a good indication of drug exposure accessible to the intestinal surface.

DISCUSSION

The drug release pattern of the solid dispersion could help understand the behavior of the formulation in different pH environments. In contrast to solid dispersion made by the solvency and drying method, the HME products make it much easier to do the *in vitro* test of drug dissolution. The importance of performing dissolution tests for the HME formulations cannot be emphasized enough. The products coming out from the HME machine output were rapidly cooled down at room temperature and solid sticks formed, short pieces of which could be cut out, weighed, and placed in the dissolution medium to start the test. Given the fact that DQ is not easily detectable in the aqueous medium because of its insolubility, the solution of 0.1 N Hydrochloric acid (HCl) combined with 10 mM Sodium Dodecyl Sulfonate (SDS) was chosen as a dissolution medium to make the released DQ measurable. For drug release from the solid dispersion containing an enteric polymer HPMC as a carrier, Phosphate-Buffered Saline (PBS) with pH 6.8 (neutral) was also used as a dissolution medium. F8 and F15 are the two optimized HME formulations. F8 containing HPMC AS-216 had an 80% of the drug dissolved within 2 hours in a neutral medium, but it took about 9 hours to dissolve the same amount of the drug in an acidic medium. This may indicate that the API will not be released in the acidic gastric cavity until it enters the intestinal environment (close to pH 6.8), which may be beneficial to drug absorption. F15 with soluplus as a carrier had more than 95% of DQ released into an acidic medium in one hour. Thus, there was no need to perform tests in a neutral medium. It is conceivable that DQ quickly released from F15 in the acidic gastric cavity can enter the intestine to be absorbed. But what percentage of the drug could get to the next journey and be absorbed was unclear. All melt-extruded formulations were evaluated by *in vitro* drug release test, but only a handful of data of formulations using HPMC or Soluplus as drug carriers were shown in the paper (1). Multiple dissolution curves from different batches were compared to see whether the pattern of the drug release had changed and if the curves of the same formulation could be overlapped to monitor the quality and the reproducibility of the extruded dispersion.HME Methods including

Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD) can help determine if there was a physical interaction of DQ with excipients through the HME process or if DQ had fused into the polymers HPMC AS (F8) or Soluplus (F15) via hot melt. Besides, the DSC and XRD patterns of material prepared by the HME process may indicate how well DQ is dispersed in the polymers to form drug particles. Within the particles, polymers are amorphous whereas drugs (API) can be crystalline or microcrystalline, amorphous, or molecular state. If DQ in the HME formulation is in crystalline form, the formulation is of poor quality. To ensure a fast drug release and bioavailability improvement, a sharp and narrow peak indicative of crystalline drug (pure DQ) should be absent or as minimal as possible in the XRD graph of HME formulation. Analytical results supported that more than 95%of HME DQ was either amorphous or in a molecular state. It could be a mixture of the two. In the case of the F8 formulation, there was only a small fraction of DQ in the crystalline form (<3%). Ideally, a solid solution (drug molecule dispersed in polymers) could be formed if the appropriate polymer/drug ratio, miscibility of polymer/drug, and HME processing were all perfectly applied. The stability of the solid state could preserve drugs from aggregation and prevent recrystallization of the molecularly dispersed drug.

The HME formulation of DQ

The stability of HME extruded dispersion was observed by measuring particle size and antimalarial activity intermittently. The particle size of F8 and F15 was found to be stable for over a year. Both formulations had potent inhibitory effects (IC50<0.5 nm) on *Plasmodium in vitro* and the potency remained unchanged 79 days after the formulations were prepared. The stability of particle size and potency of the HME dispersion suggests that DQ is thermodynamically stable post extrusion. The stability of the HME formulation was further recognized by the evidence that the DQ of F8 was intact upon being exposed to high temperature (T), high humidity, and strong light for 10 days. Pure DQ was not resistant to strong acids and alkaline after being exposed for 2 days whereas F8 DQ remained intact upon being exposed to strong acids and alkaline for 10 days. The data suggest that F8 solid dispersion is protective of DQ when it is exposed to these hazard conditions tested. The resistance of F8 DQ to strong acids may also explain the peak value of the drug dissolution curve reached only after long hours (14h) in an acidic medium. The polymers evaluated for creating DQ HME formulations are generally recognized as safe for clinical use. Polymers and surfactants selected for HME formulations are shown to be sufficient to make DQ, a poorly water-soluble API, stabilized in the glassy amorphous matrix before the solid formulation is getting touched by aqueous fluid.

Oral bioavailability, liver distribution, and liver stage *plasmodium* infection

The liver stage of malaria is an important early phase of malaria invasion of the human body. The previous pharmacokinetic study showed that in contrast to DQ microparticle suspension, DQ nanoparticle suspension orally dosed to mice produced significantly higher drug exposure levels in the liver than those in the plasma [4]. A high concentration of DQ distributed in the liver is especially important due to the liver's role in the initiation of the complex *Plasmodium* life cycle. Bottom-line, antimalarial agents need to be associated with the host cells to kill or suppress the parasites. Thus, the predominant distribution of DQ in the liver is in favor of targeting the development and multiplication of the parasites in the liver. Uninucleate sporozoites of *Plasmodium* parasites are injected into a human host when Anopheles mosquitoes bite. The sporozoites travel to the liver and invade liver cells. In the liver, the sporozoites grow, divide, and produce tens of thousands of merozoites per liver cell. *Plasmodium* multiplication in the liver can result in millions of parasite-infected cells in the host bloodstream, leading to illness or even death. On the other hand, DQ concentrations in the blood cells were much higher than those in the plasma of rats after HME DQ was orally dosed [1]. In case, merozoites invade and multiply in the red blood cells, the predominant distribution of DQ in the blood cells rather than in the plasma favors the growth inhibition of the parasites.

CONCLUSION

DQ prepared by HME was highly effective at inhibiting *Plasmodium* infection *in vitro* at both the liver stage and blood stage. The low oral dose of HME DQ was also highly efficacious against liver-stage *Plasmodium* infection in mice. HME DQ dose that was 650 folds greater than the efficacious *in vivo* dose did not result in any prominent adverse effects in mice. It is concluded that HME technology may offer a large-scale producible and environment-friendly solution to manufacture solid DQ formulation processable to tablet. The medication can be useful for preventing *Plasmodium* infections and treating malaria at the liver stage.

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