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Nanoscale Kolliphor® HS 15 micelles to minimize rifampicin self-aggregation in aqueous media

Estefanía Grotz [a, c], Ezequiel Bernabeu [a, c], Monica Pappalardo [b], Diego A. Chiappetta [a, c], Marcela A. Moretton [a, c, *]

[a] Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Cátedra de Tecnología Farmacéutica I, Buenos Aires, Argentina
[b] Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Cátedra de Farmacia Clínica y Asistencial, Buenos Aires, Argentina
[c] Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina

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ABSTRACT

Tuberculosis is a highly-deadly disease that affects both children and adults. Rifampicin, one of the "first-line" anti tuberculosis drugs, self-aggregates in aqueous solutions where the critical aggregation concentration demonstrated a temperature-dependent behavior. Interestingly, drug self-aggregation could negatively affect the development of liquid aqueous rifampicin pediatric tuberculosis formulations. Therefore, our nanotechnological strategy to minimize this effect was the rifampicin encapsulation within polymeric micelles, employing the commercially available Kolliphor® HS 15, as the micelle-former biomaterial. The results show that Kolliphor® HS 15 is able to prevent rifampicin aqueous self-aggregation and precipitation, when used at certain concentrations. In this context, our work opens the possibility of developing aqueous liquid rifampicin dosage forms for pediatric patients to improve tuberculosis treatment.

1. Introduction

Tuberculosis (TB) is a highly-deadly disease, mainly caused by *Mycobacterium tuberculosis* that affects both adults and children. Indeed, it has been reported that 140,000 children died of this infectious pathology only in 2014 [1]. TB treatment involves the daily oral administration of a combination of "first line" anti-TB drugs usually commercialized as tablets or capsules. This represents a major drawback for pediatric adherence to TB treatment. Generally, children under 7 years old have difficulties at taking pills, which is why liquid formulations are required [2]. Rifampicin (RIF) (Scheme 1) represents one of the most effective "first line" anti-TB drugs employed along the short-term (6 months) standardized TB treatment [3]. It is a limit class II drug, according to the Biopharmaceutical Classification System (BCS) [4]. RIF exhibits amphiphilic properties due to its chemical structure (Scheme 1), with very low pH-dependent aqueous solubility, and poor stability in aqueous media [5,6]. Moreover, RIF is degraded in the stomach, due to the highly acidic environment [7]. Furthermore, RIF may undergo a significant self-aggregation in aqueous media over time, which hampers the development of stable RIF oral liquid formulations, especially for pediatric TB therapy. In this framework, the employment of polymeric micelles (PMs) could be an attractive nanotechnological strategy to overcome RIF instabilization/precipitation in aqueous media.

One commercially available amphiphilic copolymer employed as a parenteral excipient in aqueous formulations is known as Kolliphor® HS 15 (Kolliphor) [8,9]. It is an amphiphilic non-ionic emulsifying and solubilizer agent with low molecular weight (~963.25 g/mol) [10]. Kolliphor consists of polyglycol mono and di-esters of 12-hydroxystearic acid along with free poly(ethylene glycol) (PEG) (~30%) (Scheme 1) [11]. It has been approved by the United States Food and Drug Administration (U.S. FDA) and it has raised special interest as a micelle-former biomaterial in the last years. Interestingly, it is currently used for enhancing aqueous solubility of poorly aqueous soluble drugs [12]. Furthermore, nowadays Kolliphor is encoded in the United States, the European and the Germany pharmacopoeias [13].

In this context, one of the mains goals of the present

* Corresponding author. Departmento de Tecnología Farmaceútica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, 956 Junín St., 6th Floor, Buenos Aires CP1113, Argentina.
E-mail address: marcelamoretton@gmail.com (M.A. Moretton).

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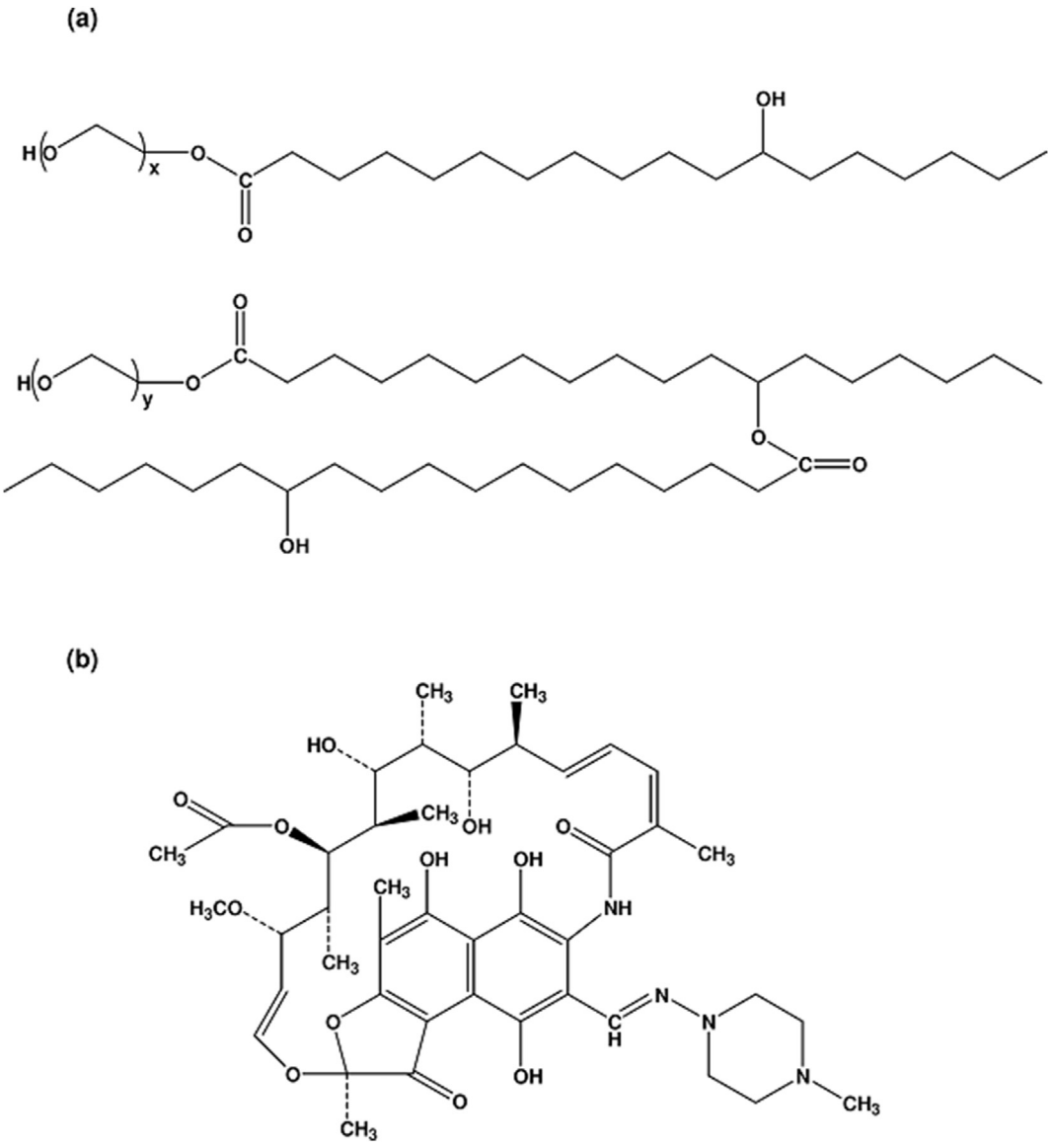

Scheme 1. Chemical structure of (a) Kolliphor and (b) RIF.

investigation was to improve RIF stability in aqueous formulations, minimizing its self-aggregation, by using PMs based on Kolliphor, for the potential development of novel pediatric liquid formulations for TB therapy.

2. Materials and methods

2.1. Materials

The materials employed consisted in polyoxyl 15 hydroxystearate (Kolliphor® HS 15, molar mass ~ 963.25 g/mol) kindly supplied by BASF (Argentina). RIF was purchased from Parafarm® (Argentina). Solvents, as acetone and *N-N*-dimethylformamide (DMF), were of analytical grade, and were used as indicated by manufacturers.

2.2. Preparation of RIF-loaded polymeric micelles

RIF-loaded PMs were prepared by a solvent-diffusion technique, employing acetone as organic solvent. Briefly, an organic solution of RIF (20–100 mg) was obtained in acetone (20 mL), with sonication to enhance its solubilization (Digital Ultrasonic Cleaner, PS-10A 50/60 Hz, China, 15 min, 25 °C). Subsequently, this solution was added dropwise to an aqueous Kolliphor dispersion (1–10% w/v) under magnetic stirring, using a programmable syringe infusion pump (1 mL/min, PC11UB, APEMA, Argentina) at room temperature. Magnetic stirring was maintained overnight to ensure acetone evaporation. Then, the volume of the resulting aqueous micellar dispersion was adjusted to 10 mL with distilled water in a volumetric flask. Immediately, samples were filtered by a clarifying filter (0.45 μm, cellulose nitrate, Microclar, Argentina) and stored in amber glass vials. Copolymer-free RIF (2 mg/mL) solutions and drug-free Kolliphor dispersions were used as controls.

On the other hand, RIF-loaded PMs were also prepared with different RIF concentrations (2.5–10.0 mg/mL), maintaining Kolliphor concentration (5% w/v), employing the same technique described above.

The concentration of RIF in every system assayed was determined by UV/Vis spectrophotometry (482 nm, 25 °C, UV-260, UV–Visible Recorder Spectrophotometer, Shimadzu, Japan)