Design of taste-masked primaquine – ion exchange resin complex intended for pediatric formulations.

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INTRODUCTION

Off Label Administration

Bitter taste when suspended in water

Ineffective treatment

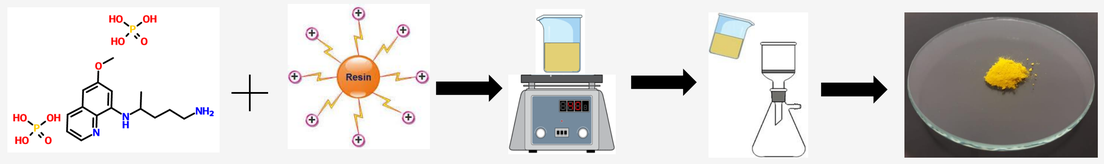
Non-acceptance of the medicine

Primaquine diphosphate (PRQ) is known for its unpleasant taste, which can lead to non-acceptance of the medicine among malaria patients under five years old, especially when it is given for a radical cure treatment of *P. vivax* and *P. ovale* over 14-day treatment.

PURPOSE

This study aims to determine the feasibility of primaquine-resin complex formation and evaluate the taste masking efficiency through an adapted dissolution test.

METHODS



Primaquine diphosphate + polacrilin potassium (PP)
Drug : resin ratio 1:2; 1:1; 2:1 (w:w)

- Resin suspended in PRQ solution (pH 5.0)
- Magnetic stirring 24h
- Room temperature

Pimaquine resinate complex

Solid state NMR

- Recycle time of 15 s,
- Spinning rate of 10.0 kHz
- Contact time of 8 ms.

DSC

- 2 – 4mg sample
- Heating rate 10ºC/min (30 – 300ºC)
- non-hermetic aluminum pan

Dissolution test

- 900mL HCl 0.1N
- pH 1.2; 37 ºC
- Paddles at 100 rpm
- UV-Vis measurement at 260nm

Taste Masking

- 500 mL artificial saliva
- pH 6.8 and 37º C
- Paddles 50 rpm
- UV probe measurement at every 5 seconds for 3 minutes.

RESULTS

Drug Load Efficiency

Table 1: PRQ loading efficiency on ion exchange resin (IER) complex.

Drug:resin ratio (w:w)	Drug load eficiency (%)	Conclusion
1:2	95.09 ± 0.005	✗
1:1	91.07 ± 1.03	✓
2:1	25.30 ± 0.02	✗

The drug-to-resin ratio of 1:1 (w:w) demonstrated high drug loading efficiency at 91.07% ± 1.03%. The other ratios resulted in excess PRQ (2:1) or IER (1:2) after 180 minutes.

Differential scanning calorimetry analysis

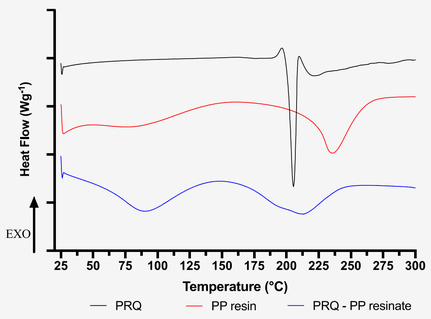


Figure 1: DSC curves of PRQ, PP resin and PRQ-PP resinate

The PRQ resinate successfully achieved drug amorphization, which was confirmed by the absence of the endothermic event of the PRQ melting point (206ºC) when compared to the salt form of the drug.

Dissolution test and Taste Masking

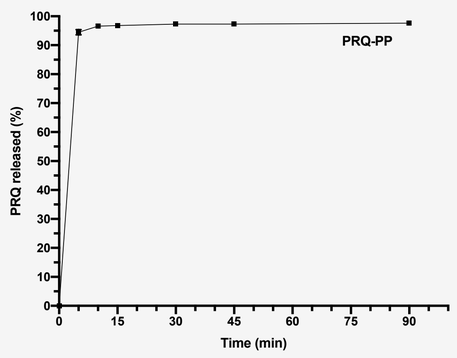


Figure 2: Dissolution profile of PRQ-PP resinate

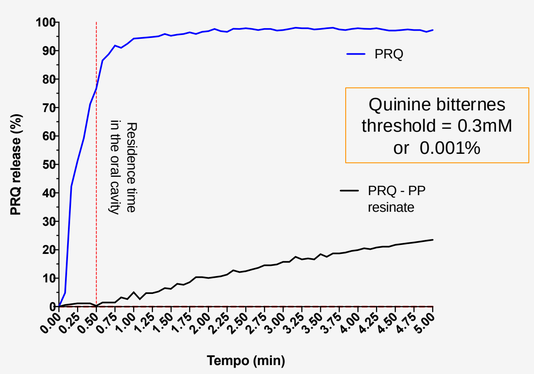


Figure 3: Taste masking efficiency analysis

In the pH 1.2 dissolution test, the PRQ-complex exhibited a rapid drug release, with 94.5% ± 0.87% released in the first 5 minutes, suggesting no bioavailability issues in acidic conditions. Furthermore, in simulated saliva at pH 6.8, the resinate only released approximately 1.97% in 30 seconds, demonstrating effective taste masking due to the minimal amount of PRQ released in this condition.

Solid-state NMR

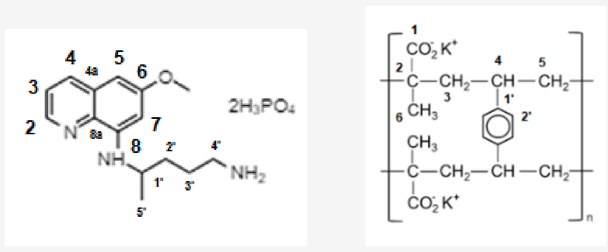


Figure 4: Structural formula of PRQ and PP ion exchange resin.

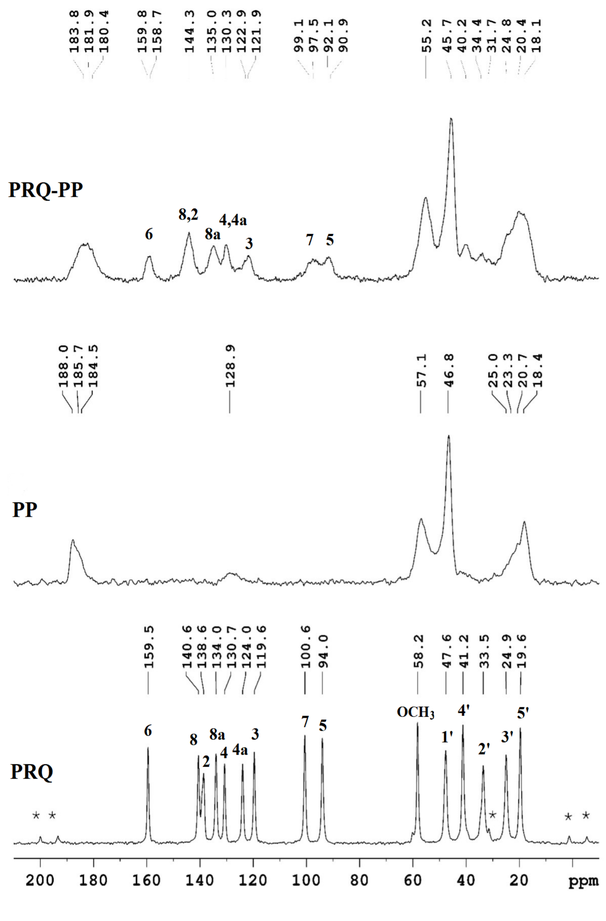


Figure 5: ^{13}C CPMAS NMR spectra of the samples evaluated. The carbon signals are numbered following the structures presented in Fig. 4.
(*) denotes spinning sidebands.

Table 2: Chemical shifts (δ, ppm) of PRQ, PP resin and PRQ-PP resinate.

CARBON	PRQ						PP resin[a]	PRQ-PP resinate[a]
	δ, ppm[a]	δ, ppm[b]	δ, ppm[c]	δ, ppm[d]	δ, ppm[e]	δ, ppm[f]	δ, ppm	δ, ppm
C6	159.5	162.9	157.9	159.6	160.6	158.1	-	159.0
C8	140.6	141.1	141.8	145.2	146.4	149.7	-	144.0*
C2	138.6	141.4	141.6	144.3	145.2	138.2	-	144.0*
C8a	133.4	126.6	132.3	135.5	135.5	133.0	-	134.7
C4	130.8	147.3	126.2	134.8	135.5	128.1	-	130.2
C4a	123.9	133.8	125.0	130.0	130.2	127.2	-	121.7*
C3	119.6	124.3	123.1	121.8	121.7	122.1	-	121.7*
C7	100.7	106.2	105.5	96.9	96.5	104.5	-	97.7
C5	94.0	97.6	102.1	91.9	96.1	102.1	-	91.6
CH_3-O	58.2	58.5	55.4	55.2	55.8	55.4	-	Overlap wtih PP
C1'	47.6	51.4	51.8	48.1	52.8	51.8	-	Overlap with PP
PC4'	41.2	42.4	43.3	41.7	42.0	41.5	-	39.7**
C2'	33.5	34.7	29.8	34.1	34.6	29.8	-	33.6**
C3'	24.9	26.2	23.4	29.3	31.1	25.6	-	24.6*
C5'	19.6	21.2	19.8	20.5	21.1	19.8	-	Overlap with PP
C1 ($CO_2^-K^+$)	-	-	-	-	-	-	186.5; 185.6	184.2; 182.4; 180.6
C1'arom.	-	-	-	-	-	-	148.4	
C2'arom.	-	-	-	-	-	-	129.6; 127.8	
C2, C3,	-	-	-	-	-	-	57.4; 46.8	55.5; 45.7
C4, C5							57.4; 46.8	55.5; 45.7
C6	-	-	-	-	-	-	30 - 10	

[a]Solid-state ^{13}C CPMAS, this work; [b]Solution ($CDCl_3$) ^{13}C diprotonated (Clark et al.,1981); [c] simulation diprotonated, Topspin 4.0.8.; [d]Solution ($CDCl_3$) free base (Clark et al. 1981); [e]simulation, free base, ChemBioDraw Ultra 12.0 (Brondz, 2012); [f]simulation, free base, Topspin 4.0.8.
* loss of definition; ** increase in width.

Table 3: Chemical shifts (δ, ppm), and relaxation times T_{CH} and T1ρH obtained for samples PRQ, PP and PRQ-PP resinate.

CARBON	PRQ			PP resin			PRQ-PP resinate		
	δ, ppm[a]	T_{CH} (μs)	T1ρH (ms)	δ, ppm	T_{CH} (μs)	T1ρH (ms)	δ, ppm	T_{CH} (μs)	T1ρH (ms)
C6	159.5	n.d.	n.d.	-	-	-	159.0	n.d.	n.d.
C8	140.6	636	265	-	-	-	144.0*	327	12.3
C2	138.6	1220	336	-	-	-	144.0*	327	12.3
C8a	133.4	483	246	-	-	-	134.7	n.d.	n.d.
C4	130.8	n.d.	n.d.	-	-	-	130.2	n.d.	n.d.
C4a	123.9	n.d.	n.d.	-	-	-	121.7*	n.d.	n.d.
C3	119.6	511	251	-	-	-	121.7*	n.d.	n.d.
C7	100.7	507	246	-	-	-	97.7	n.d.	7.3
C5	94.0	497	231	-	-	-	91.6	427	9.8
CH_3-O	58.2	597	304	-	-	-	Overlap with PP	-	-
C1'	47.6	402	184	-	-	-	Overlap with PP	-	-
C4'	41.2	373	183	-	-	-	39.7	241	6.1
C2'	33.5	341	181	-	-	-	33.6	388	n.d.
C3'	24.9	402	191	-	-	-	24.6*	345	6.7
C5'	19.6	n.d.	n.d.	-	-	-	20.4*	266	9.4
C1 ($CO_2^-K^+$)	-	-	-	186.5	1930	9.7	182.9	741	8.4
C1'arom.	-	-	-	148.4	n.d.	n.d.	n.d.	n.d.	n.d.
C2'arom.	-	-	-	129.6	n.d.	n.d.	n.d.	n.d.	n.d.
				127.8	n.d.	n.d.	n.d.	n.d.	n.d.
C2, C3, C4, C5				~57	99	9.4	n.d.	n.d.	n.d.
C2, C3, C4, C5	-	-	-	~47	640	9,0	n.d.	n.d.	n.d.
C6	-	-	-	18	355	11.7	19.3	266	9.4

[a] assignment suggested. * signal not properly defined

NMR analysis showed that all the carbon signals could be assigned, including those linked to the IER polacrilin potassium. A strong increase in the width of quinoline moiety, and a decrease in T1ρH values confirmed the interaction between PRQ and IER moieties.

CONCLUSION

- The results showed that complexation with ion exchange resins does not entirely remove primaquine's bitter taste but significantly reduces its perception.
- The complexation of PRQ with IER presented a high drug loading efficiency and the complexation was demonstrated by DSC and by solid - state NMR analysis.
- Proceeding with the following development stages is feasible to create a new and palatable oral formulation of primaquine resinate for children.

ACKNOWLEDGEMENT

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