Determining the Bio-distribution of Colloidal Iron Drug Products in Rats by Inductively Coupled Plasma Mass Spectrometry (ICP-MS)

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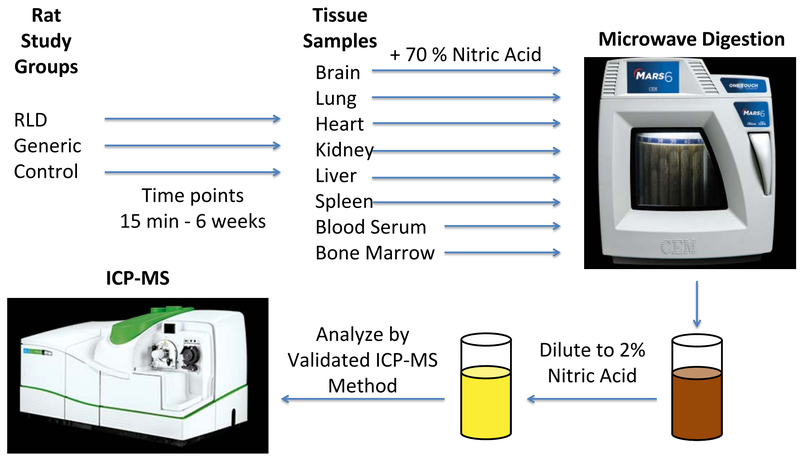
Introduction

Parentally administered colloidal iron products are used in iron replacement therapy and are internalized by the phagocytic cells, where the iron ions become part of the intracellular iron pool. Iron is stored in the cell as ferritin or hemosiderin, or mobilized as transferrin bound iron. Iron release from the colloidal iron products and its subsequent distribution in the body are size and surface dependent, with differences in core size and carbohydrate chemistry determining pharmacologic and bioactivity differences such as clearance, iron release rate and maximum tolerated dose. In the current study, we evaluate the iron biodistribution of Ferrlecit® (sodium ferric gluconate) and its generic copy in major organs of Sprague Dawley rats. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) methods were used to quantify the total iron distribution to these tissues. Across the time points, no difference was seen in biodistribution between the reference and generic drugs in any of the organs evaluated.

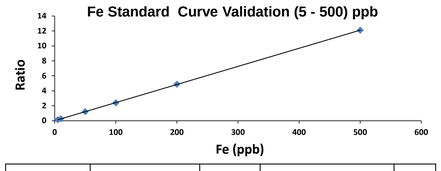
Method

The biodistribution study was conducted in house utilizing normal Sprague Dawley rats. The study was conducted on a single dose of 40 mg/kg of Ferrlecit® for the reference listed drug (RLD) group, 40 mg/kg of generic sodium ferric gluconate for the generic drug (GEN) group, and no dose for the control (Ctrl) group. Each group consisted of 42 rats, six rats were sacrificed at each time point over seven time points consisting of 15 minutes, 1 hour, 8 hours, 1 week, 2 weeks, 4 weeks, and 6weeks. Eight biodistribution samples were collected from each rat during sacrifice, the brain, lungs, heart, spleen, kidneys, liver, blood serum, and bone marrow. The whole tissue samples were weighted and accurate portions of these tissues ranging between 250 mg – 400 mg were digested in 70% nitric acid by microwave digestion. The blood was centrifuged and plasma was used for iron analysis to remove hemoglobin as a contamination source of iron. 1 mL of plasma was digested in 70% nitric acid by microwave digestion for this study. Since, bone marrow was exceptionally difficulty to acquire the entire sample was used for analysis, and 70% nitric acid was used to extract the bone marrow sample from the collection tube before microwave digestion. The digested samples were then diluted to 2% nitric acid, a workable concentration for Inductively Coupled Plasma Mass Spectrometry (ICP-MS) methods, and analyzed by ICP-MS.

Study Design

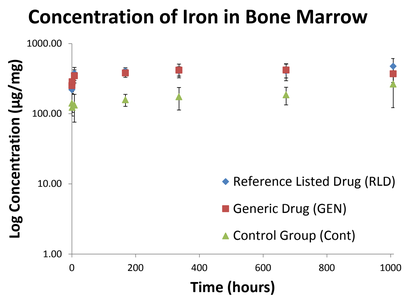


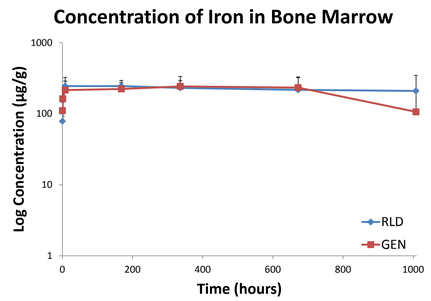
Validation Day One				
	QC-5 ppb	QC-10 ppb	QC-200 ppb	QC-500 ppb
Average	4.7	48.2	196.2	488.8
Stdev.	0.2	0.3	0.2	2.0
CV(%)	93.5	96.4	98.1	97.8
Validation Day Two				
Average	4.60	48.38	197.07	494.6
Stdev.	0.22	0.28	0.50	6.2
CV(%)	91.90	96.76	98.54	98.9
Validation Day Two				
Average	5.33	49.31	196.87	485.3
Stdev.	0.06	0.15	0.83	4.6
CV(%)	106.63	98.61	98.43	97.0

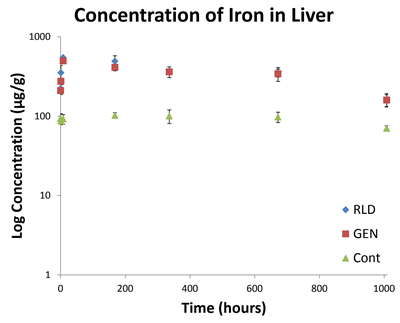


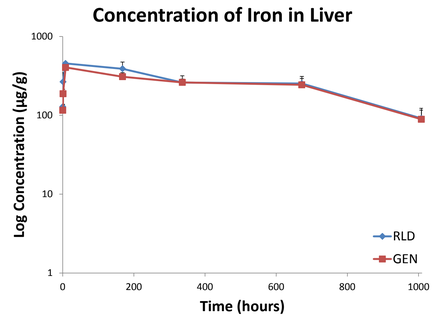
Calibration sets	Linear Range (Fe ppb)	Calibrators	Correlation coefficient (r^2)	Slope
1	5-500	6	0.9999	0.0246
2	5-500	6	0.9999	0.0244
3	5-500	6	0.9999	0.0242

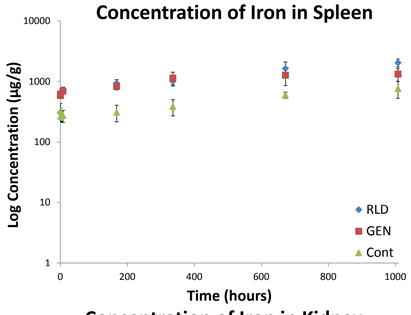
Result in High Accumulation Organs

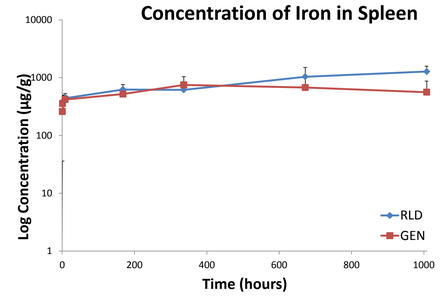


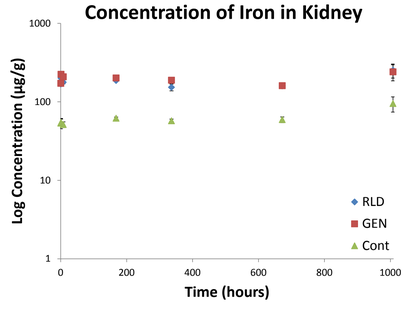


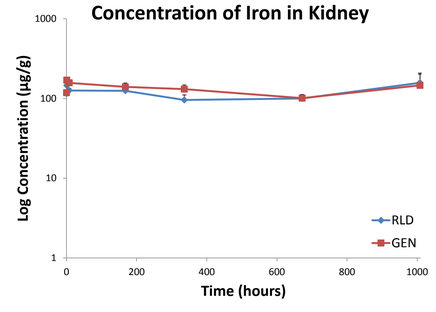




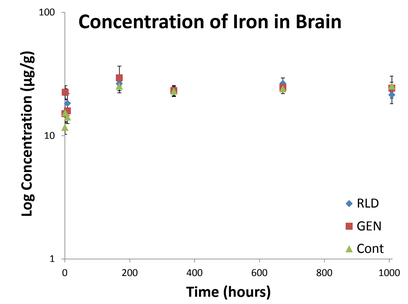


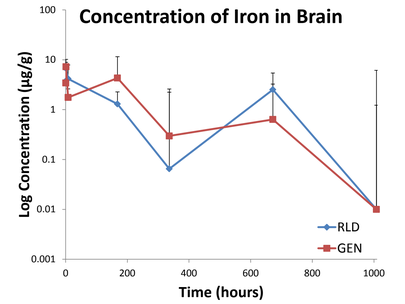


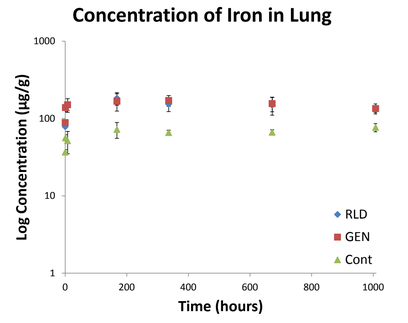


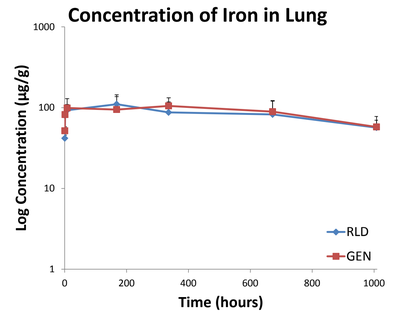


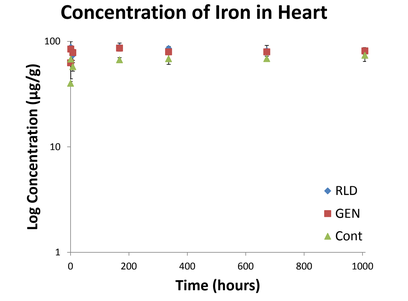
Results in Low or No Accumulation Organs

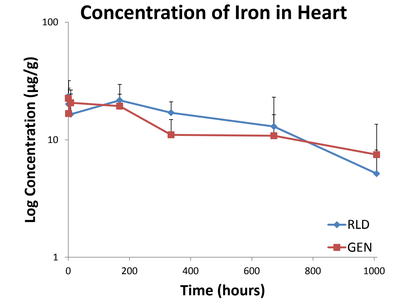


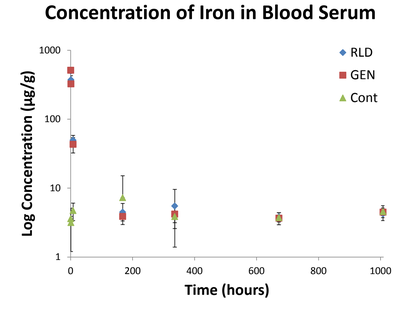


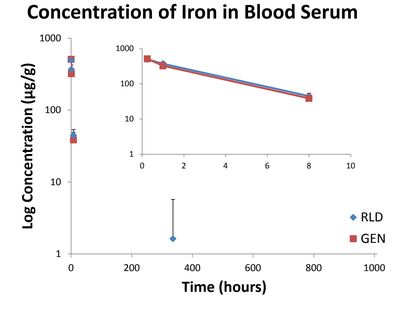












Observations

- The target organ, bone marrow, served as a reservoir for iron delivered by the drug
- The liver, spleen, and kidneys also served as reservoirs for the excess drug iron
- Blood serum clearance was fast; no drug iron could be measured after eight hours
- No significant distribution/transport of iron to the brain

Disclaimer

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

Conclusion

- No significant difference in overall biodistribution was observed between the reference listed drug and generic drug groups; especially in the target organ (bone marrow)

Acknowledgements

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