University of California San Diego / School of Medicine / Division of Infectious Diseases

Wirelessly Observed Therapy (WOT): a new paradigm in TB therapy monitoring.

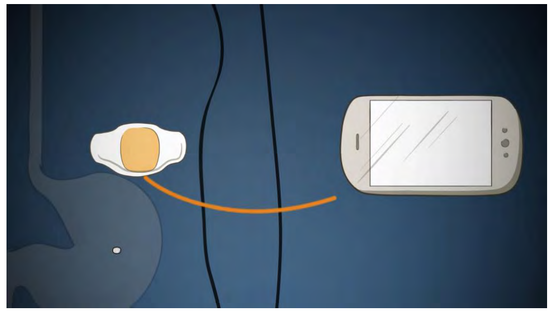
Browne, S., Haubrich, R., Moser, K., Tucker, A., Vaida, F., Peloquin, C., Benson, C.

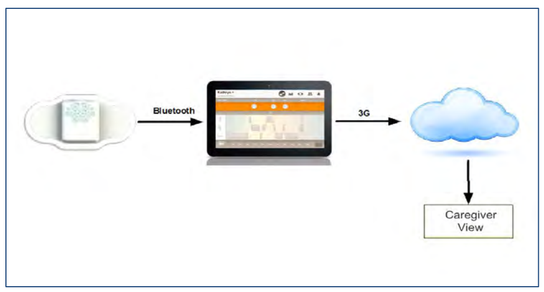
BACKGROUND

Directly Observed Therapy (DOT) is universally recommended for TB treatment adherence, but DOT is resource intensive, expensive and unfeasible in resource-limited settings.[1]

Novel Wirelessly Observed Therapy (WOT) technology provides date- & time-stamped recording of medication ingestions via an ingestible sensor and monitor patch worn on the patient's torso.

Figure 1. Wirelessly Observed Therapy. How it works.





Sensor activates upon becoming wet in stomach. Biogalvanic signal transmitted to sensor patch worn on the torso. Patch stores the data and transmits it to a mobile device via Bluetooth. From the mobile device the data is sent securely encrypted to the Internet over the 3G network.

OBJECTIVES

To determine whether over-encapsulation (OE) of Rifamate and Rifinah with integration of the ingestible sensor(IS) was safe and bioequivalent to standard drug.

To determine the Positive Detection Accuracy (PDA) of the WOT system as compared to standard in person DOT.

To determine the percentage of correctly identified WOT and DOT doses recorded (number observed/number prescribed).

Figure 2. The first ever edible sensor, over-encapsulated with Rifamate

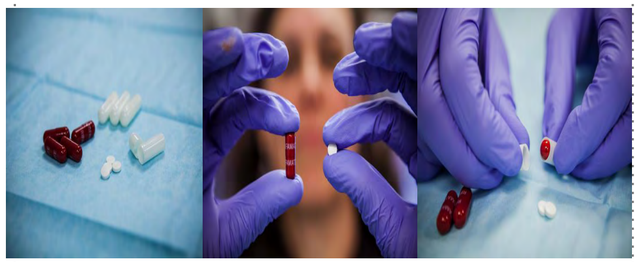
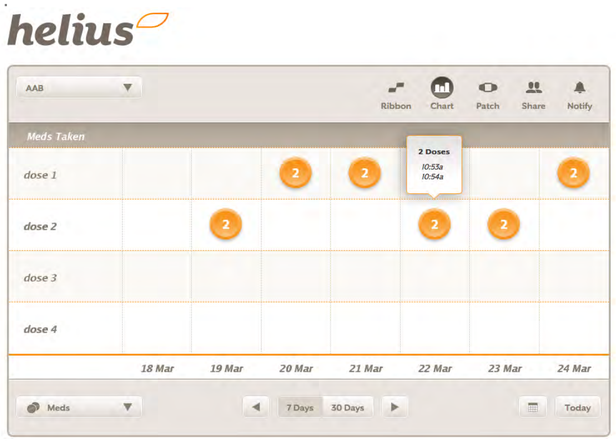


Figure 3. DOT worker's online view.



Online viewing platform allows healthcare worker to verify ingestions for multiple patients in one location. Ingestions are easily identifiable by date and time stamp. Patch function and wear time can also be checked and monitored.

METHODS

- We integrated the ingestible sensor (IS) with Rifamate and Rifinah, the combination dosage forms of isoniazid (INH) and rifampin (RIF), via over-encapsulation (OE) with Gelucaps and performed dissolution tests.
- We conducted a randomized bioequivalence (BE) study in 12 patients with active TB during the continuation phase comparing IS-Rifamate to its native form.
- INH and RIF assayed using validated HPLC methods, and PK parameters analyzed using non-compartmental methods (Phoenix/WinNonlin software).
- We measured the Positive Detection Accuracy (PDA) of the WOT system using IS-Rifamate by comparing WOT ingestions recorded when doses were given under DOT (n=280)
- We evaluated WOT performance in comparison to DOT in 14 active TB patients by comparing the percentage of confirmed doses delivered by WOT with those delivered by DOT (number observed/ number prescribed)

RESULTS

Figures 4a and b. Dissolution Study Results

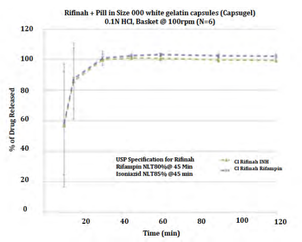


Fig. 4a. Dissolution of co-encapsulated Rifinah 150mg/300mg meets the individual pharmacopeia requirements for dissolution for isoniazid and rifampin respectively.

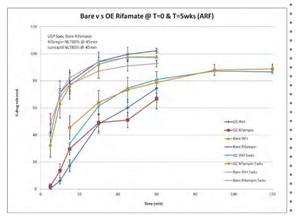


Fig. 4b.Dissolution of OE IS-Rifamate (100mg/300mg) only reached 85-90% at 120mins.

Table 1. Absorption characteristics for OE IS-Rifamate versus native form analyzed using non-compartmental methods

Medication Regime	Cmax (mcg/ml) Median value	AUC$_{0\text{-}12hr}$ (mcg/ml) Median value
Native Rifamate: RIF	12.12	45.19
NH	3.85	13.34
OE IS-Rifamate: OE RIF	11.79	43.76
OE NH	4.27	12.50

Pharmacokinetic Analysis: OE IS-Rifamate versus native form(NR). INH and RIF were shown to be bioequivalent using the population method ratio test (95% confidence level).

Figure 5A. PK of INH OE vs. Native

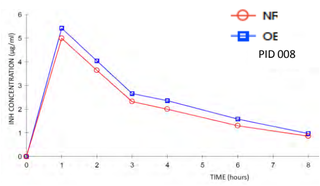


Figure 5B. PK of RIF OE vs. Native

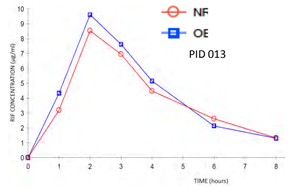


Table 2. Positive Detection Accuracy: WOT is equivalent to DOT

Three relative proportions of WOT observations were calculated for each patient. Their summaries are presented separately.

Measure (1): $\frac{\#\text{ of WOT ingestions recorded}}{\#\text{ of DOT observations}}$ (includes only those observations that have a record of DOT.)

Table 4: Summary of WOT and DOT measures, estimated by percent

Measure		Statistic
(1) $\frac{\#\text{ of WOT ingestions recorded}}{\#\text{ of DOT observations}}$ (days with DOT only)	Mean (SD)	98.4 (2.57)
	Median (IQR)	100 (96.2 – 100)
	Range	93.8 – 100

SD = standard deviation, IQR = interquartile range

Figure 6. WOT is equivalent to DOT

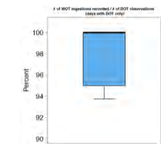


Table 3. The total number of WOT observations versus total numbers of DOT doses

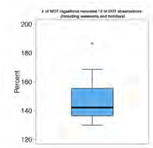
Measure (2): $\frac{\#\text{ of WOT ingestions recorded}}{\#\text{ of DOT observations}}$ (all WOT observations, including weekends or CA state holidays.)

Table 5: Summary of WOT and DOT measures, estimated by percent

Measure		Statistic
(2) $\frac{\#\text{ of WOT ingestions recorded}}{\#\text{ of DOT observations}}$	Mean (SD)	148 (16.8)
	Median (IQR)	142 (136 – 155)
	Range	130 – 187

SD = standard deviation, IQR = interquartile range

Figure 7.WOT outperformed DOT



CONCLUSION

- Over–encapsulation with IS was safe and bioequivalent to standard drug.
- The PDA confirms WOT is highly accurate.
- WOT is delivered daily and confirmed more drug doses ingested than DOT overall. Daily dosing provides higher total dose delivery and maintains higher continuous drug levels.[2,3]
- WOT represents a new paradigm in TB therapy monitoring.

BIBLIOGRAPHY

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ACKNOWLEDGEMENTS

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