A Simplified Approach for Compounding Slow-Release Capsules in Pharmacy Practice

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Background

- Physicians often prescribe slow-release capsules to increase patient adherence and improve pharmacotherapy. However, due to changes in excipient(s) or their ratio, the release kinetics of these SR formulations might vary thus posing a significant risk of toxicity.
- Compounded hormone preparations are often prescribed by physicians in the United States. The compounded preparations may be called Slow-Release (SR) capsules, but do we really know the exact release kinetics and the quality of the preparations?
- Formulation development for SR capsule dosage forms requires proper knowledge and training of the compounder and an appropriate facility.

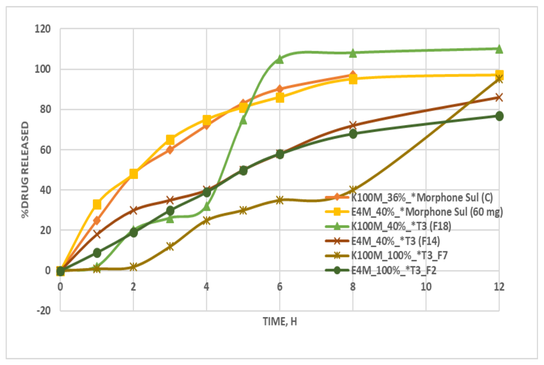

Figure 1. Release profile of different drugs from the matrix containing 33% to 100% of HPMC 2910 or HPMC 2208 (Ref.1-5)

Hypothesis

- In the current 503A pharmacy setting (traditional compounding pharmacy), doing research to develop SR formulations is impractical.
- In this context, pharmacists can play a significant role by preparing and testing different strengths of drug excipient blends for SR preparations by using a simple Alligation Method in a 503B compounding pharmacy (an outsourcing facility) and distribute these blends to 503A pharmacies to compound SR capsules/tablets.

Methods

- To test this novel concept, we formulated different strengths of drug excipient mixtures for thiamine HCl SR preparations using 40% HPMC 2208 and Lactose by both dry mix and wet granulation method.
- To characterize the formulations, we have developed a high-performance liquid chromatography (HPLC) method.
- Chromatographic condition: Detection Wavelength 280 nm, 1mL/min Flow rate, Isocratic: Solvent A (60% Water: MeOH: GAA= 73:27:1) and Solvent B (40% MeOH)
- We have evaluated the release kinetics in water using USP dissolution apparatus 2 and quantified the amount of drug release through HPLC.

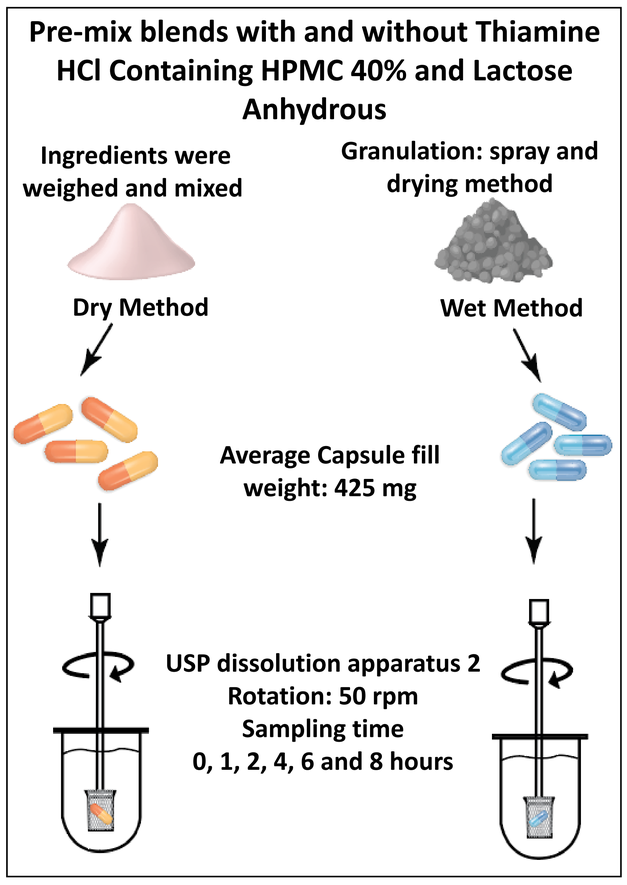

Figure 2. Research work-flow diagram

Approaches

API/ Excipients	Pre-mix 1 (%)	Pre-mix 2 (%)
HPMC	40	40
Lactose	13	60
TH	47	0

Table 1: Formulations of Pre-mix blends

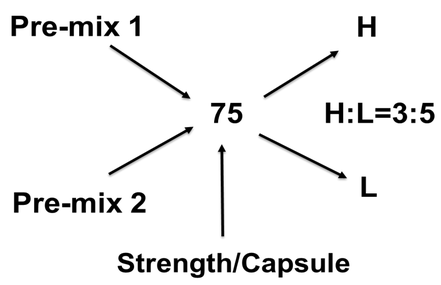

Figure 3. Alligation Method used for the target Dose

Results

- Generation of standard curve from different concentration of thiamine hydrochloride (TH)

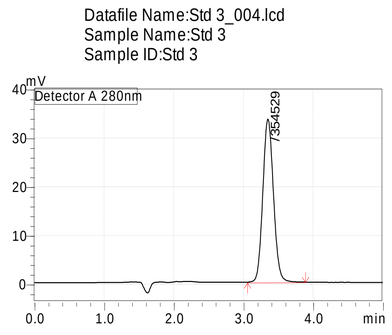

Figure 4. HPLC Chromatogram for TH standard run

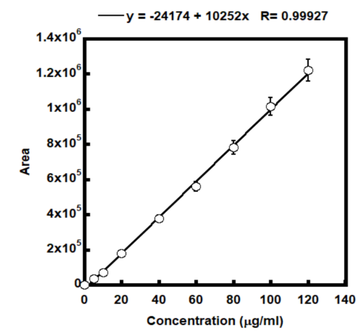

Figure 5. Standard Curve for different conc. of TH

Dissolution study

- After collection of dissolution samples from different time points for both 75mg- and 100mg doses capsules, cumulative percentages of drug release were calculated

Time points (Hour)	% of Drug Release			
	100 mg/Capsule		75 mg/Capsule	
	Dry-M	Wet-M	Dry-M	Wet-M
0	0	0	0	0
1	20.7	37.3	21.2	38.7
2	34.1	59.6	35.6	64.1
4	69.8	84.1	71.7	90.2
6	88.6	93.9	92.2	97.8
8	99	97.4	101	100

Table 2: % of drug release from different formulations at different time points

Comparison of release kinetics between two different methods of granulation

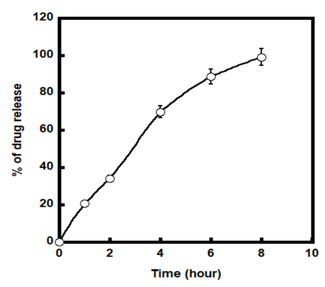

Figure 6 A. % of drug release from 100 mg Capsules

Dry mixing method

% of drug release for first few hours was not significant in comparison to wet method

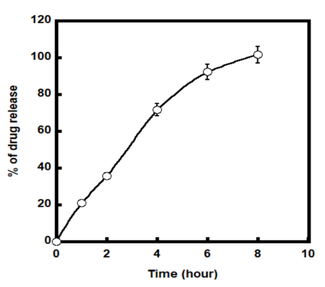

Figure 6 B. % of drug release from 75 mg Capsules

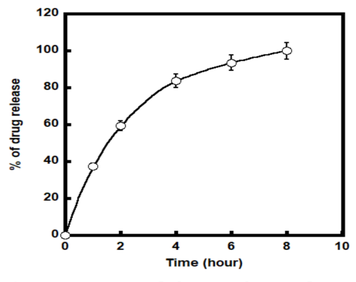

Figure 7 A. % of drug release from 100 mg Capsules

Wet granulation method

More consistent release pattern was observed in comparison to dry method

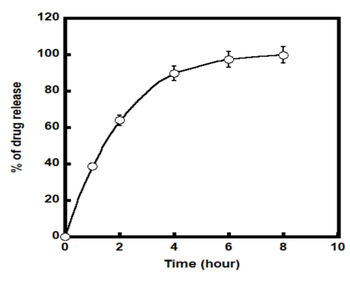

Figure 7 B. % of drug release from 75 mg Capsules

Observations

- % of drug released from both 75 mg and 100 mg capsules prepared by dry mix and wet granulation methods increasing consistently and followed the same pattern.
- Initially (at 1 and 2-hour time points), the % drug release from the 75 mg and 100 mg capsules prepared by the wet granulation method were significantly higher than the dry mix method.
- 100% of the drug was released by 8 hours for both dry and wet methods.
- The results of the thiamine hydrochloride SR compounded preparation from this study confirm our hypothesis.

Conclusion

We suggest providing different premix blends distributed by a 503B outsourcing facility per the US FDA regulations to 503A pharmacies to compound SR capsules. This approach will ensure appropriate prescriber dosing, adequate release profiles, and quality for sufficient efficacy and patient safety.

References

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