The importance of *in vitro* discriminatory tests in the development of a sublingual dosage form of TNX-102 SL (Cyclobenzaprine HCl) tablets

TNX-102 SL is an investigational drug and has not been approved for any indication.

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INTRODUCTION

The formulation of cyclobenzaprine HCl contained in TNX-102 SL has been designed specifically for sublingual administration. Earlier clinical studies indicated that the addition of a basifying agent was necessary for efficient transmucosal absorption. TNX-102 SL formulation with added dibasic potassium phosphate resulted in higher levels of exposure during the first 2 hours after dosing, less exposure 8 to 24 hours after dosing and reduced exposure to an active, persistent (long half-life), primary metabolite (norcyclobenzaprine) as a result of bypassing first-pass hepatic metabolism. The PK profile of TNX-102 SL was designed for bedtime dosing to target sleep disturbance while reducing the risk of daytime somnolence.

The achievement of transmucosal delivery was enabled by the discovery and development of a eutectic of Cyclobenzaprine HCl and Mannitol. The *in vitro* techniques used to assess and control absorption studied were dissolution, disintegration and wetting time. These *in vitro* tests with emphasis on sublingual absorption challenged the discriminatory behaviour and assessed the impact of particle size, excipient variation and compression force.

METHODS

The dissolution test is performed as per USP <711>, EP 2.9.3. Due to Cyclobenzaprine HCl pKa of 6.8, a pH 4.0 Citrate buffer was selected as the medium. As the tablets are small, a 150mL dissolution vessel is used with results recorded at 5,10,30, and 60mins @50RPM and infinity (additional 30 mins @250RPM), to confirm the complete profile.

Disintegration testing is conducted using a verified method in accordance with USP <701> and EP 2.9.1. The time to disintegrate is recorded in seconds.

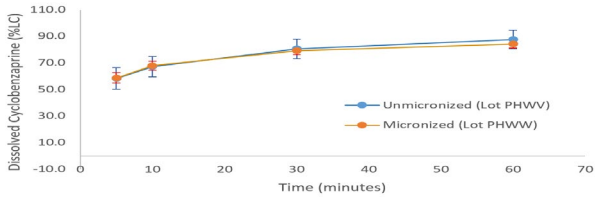
Wetting time is determined by visual examination. It is an in-house developed method which measures the elapsed time for a tablet to become fully wetted or saturated when in contact with water. The wetting time is recorded in seconds.

RESULTS SUMMARY

Table 1: Statistical Summary of the Results

Variable	Disintegration	Wetting Time	Dissolution Similarity Factor (F2)
Compression Force	Discriminatory y= 1.7x + 4.1; r^2=0.87	Discriminatory Y = 3.0x + 7.4; r^2=0.96	No Difference
Particle size	Discriminatory p = 0.0001	Discriminatory p < 0.0001	No difference
Pearlitol Flash	Discriminatory p < 0.0001	Discriminatory p < 0.0001	No difference
Crospovidone	No difference p = 0.03	No difference p = 0.05	No Difference
Sodium Stearyl Fumarate	No difference p = 0.80	No difference p = 0.04	No Difference
Potassium Phosphate Dibasic	No difference p = 0.34	Discriminatory p = 0.01	No difference

IMPACT OF DRUG SUBSTANCE PARTICLE SIZE



	Micronized DS (Patheon Lot PHWW)	Unmicronized DS (Patheon Lot PHWV)
	Disintegration Time (seconds)	
Mean	25	8
Std. Dev	6	3
RSD (%)	26	34
	Wetting Time (seconds)	
Mean	45	25
Std. Dev	4	3
RSD (%)	8	11

In summary, differences between TNX-102 SL tablets prepared with micronized versus unmicronized cyclobenzaprine HCl are detectable by USP <701> disintegration testing and the Wetting Time test, but not by dissolution. Tablets prepared with micronized drug substance disintegrated and wetted more slowly than their unmicronized counterparts. The smaller and more uniform particle size for micronized cyclobenzaprine results in the formation of smaller channels through which moisture may traverse and activate the disintegrant.

EXCIPIENT CONTENT VARIATION

Excipient	% of Target	Dissolution (%) 5 mins	10 mins	30 mins	Disintegration Time (secs)	Wetting Time (secs)
Crospovidone	80	71	81	91	10	22
	120	61	72	85	18	38
Pearlitol Flash	80	63	83	97	20	34
	120	57	81	97	12	24
Sodium Stearyl Fumarate	80	63	73	84	14	18
	120	60	76	90	14	21
Potassium Phosphate Dibasic	80	64	74	86	13	23
	120	62	71	84	15	19

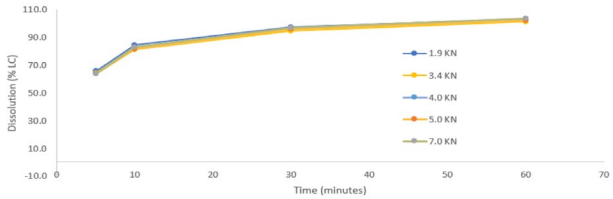
No differences are noted in dissolution profiles for tablets prepared with 80% versus 120% target Crospovidone concentration in the TNX-102 SL (2.8 mg) formulation, while slight differences are noted in wetting and disintegration data, these do not reach statistical significance at the 99% level.

In summary, differences between TNX-102 SL tablets prepared with 80% versus 120% the target concentration of Pearlitol Flash® are detectable by disintegration testing and the Wetting Time test, but not by dissolution. Tablets prepared with 80% Pearlitol Flash both disintegrated and wetted more slowly than those containing 120% Pearlitol Flash.

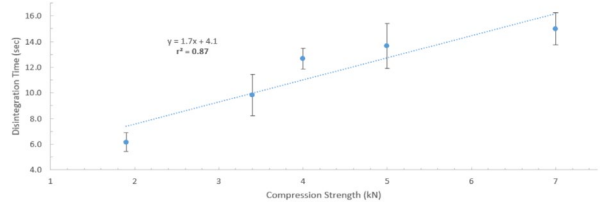
No differences are noted in dissolution, disintegration or wetting time for tablets prepared at 80% versus 120% the target concentration of sodium stearyl fumarate in the TNX-102 SL (2.8 mg) formulation.

In summary, differences between TNX-102 SL tablets prepared with 80% versus 120% potassium phosphate dibasic are detected using the Wetting Time test but not the dissolution or USP disintegration tests. Wetting time is slower for tablets prepared at the 80% potassium dibasic phosphate level.

COMPRESSION FORCE VARIABILITY



Compression Force	Disintegration Time (seconds) of TNX-102 SL Tablets Compressed at 1.9 kN	3.4 kN	4.0 kN	5.0 kN	7.0 kN
Mean	6	10	13	14	15
Std. Dev	1	2	1	2	1
RSD (%)	12	16	6	13	8



Compression Force	Wetting Time (seconds) of TNX-102 SL Tablets Compressed at 1.9 kN	3.4 kN	4.0 kN	5.0 kN	7.0 kN
Mean	14	16	20	22	29
Std. Dev	1	1	1	3	4
RSD (%)	5	7	7	12	14

In summary, variations in compression strength do not impact the dissolution profile for TNX-102 SL (2.8 mg) tablets. However, linear relationships are observed between disintegration time and wetting time versus compression strength. It should be noted that the slope of change is greater for wetting time than for USP disintegration time and the strength of the correlation is also improved. This indicates that wetting time data will produce a more sensitive measure of compression strength variations during the manufacture of TNX-102 SL (2.8 mg) tablets.

DISCUSSION

Based upon the data, summary in Table 1, the dissolution test does not discriminate between tablets made with intentional modifications to particle size, excipient content or compression strength. Both Disintegration Time and Wetting Time are sensitive to differences in particle size, Pearlitol Flash and compression strength at the 99% level (*i.e.* $p \leq 0.01$).

Disintegration and wetting time tests are proposed for quality control of TNX-102 SL sublingual tablets in lieu of the dissolution test in accordance with ICH Q6A Decision Tree #7 .

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