**UNITED STATES**
**SECURITIES AND EXCHANGE COMMISSION**
**Washington, D.C. 20549**

# FORM 8-K

**CURRENT REPORT**

**Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**

**Date of report (date of earliest event reported): September 23, 2024**

# TONIX PHARMACEUTICALS HOLDING CORP.

**(Exact name of registrant as specified in its charter)**

| **Nevada** | **001-36019** | **26-1434750** |
|---|---|---|
| **(State or Other Jurisdiction of Incorporation)** | **(Commission File Number)** | **(IRS Employer Identification No.)** |

26 Main Street, Chatham, New Jersey 07928
**(Address of principal executive offices) (Zip Code)**

**Registrant's telephone number, including area code:** (862) 904-8182

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

| Title of each class | Trading Symbol(s) | Name of each exchange on which registered |
|---|---|---|
| Common Stock | TNXP | The NASDAQ Capital Market |

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

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**Item 7.01 Regulation FD Disclosure.**

On September 23, 2024, Tonix Pharmaceuticals Holding Corp. (the "Company") announced the presentation of data in two oral presentations and a poster presentation at the 11th Global Conference on Pharmaceutics and Drug Delivery Systems held September 19-21, 2024 ("PDDS 2024") which highlighted the proprietary formulation technology and pharmacokinetic properties of the Company's TNX-102 SL (sublingual cyclobenzaprine HCl) product candidate. A copy of the press release which discusses this matter is furnished hereto as Exhibit 99.01, and incorporated herein by reference. Copies of the oral presentations and poster are furnished hereto as Exhibits 99.02, 99.03 and 99.04, and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.01, 99.02, 99.03 and 99.04 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

**Item 8.01. Other Events.**

On September 23, 2024, the Company announced the presentation of data in two oral presentations and a poster presentation at PDDS 2024 which highlighted the proprietary formulation technology and pharmacokinetic properties of TNX-102 SL.

*Forward- Looking Statements*

This Current Report on Form 8-K contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the Company's product development, clinical trials, clinical and regulatory timelines, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth opportunities and other statement that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's current beliefs and assumptions.

These statements may be identified by the use of forward-looking expressions, including, but not limited to, "expect," "anticipate," "intend," "plan," "believe,"

"estimate," "potential," "predict," "project," "should," "would" and similar expressions and the negatives of those terms. These statements relate to future events or our financial performance and involve known and unknown risks, uncertainties, and other factors which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company's filings with the SEC. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

**Item 9.01 Financial Statements and Exhibits.**

(d)

| Exhibit No. | Description. |
|---|---|
| 99.01 | Press Release of the Company, September 23, 2024 |
| 99.02 | Mannitol as Eutectic Forming Agent for Improved Sublingual Delivery of Cyclobenzaprine HCl |
| 99.03 | Pharmacokinetic Properties of TNX-102 SL, a Sublingual Formulation of Cyclobenzaprine Hydrochloride |
| 99.04 | The Importance of In Vitro Discriminatory Tests in the Development of a Sublingual Dosage Form of TNX-102 SL (Cyclobenzaprine HCl) Tablets |
| 104 | Cover Page Interactive Data File (embedded within the Inline XBRL document) |

**SIGNATURE**

Pursuant to the requirement of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

**TONIX PHARMACEUTICALS HOLDING CORP.**

Date: September 23, 2024

By: /s/ Bradley Saenger
Bradley Saenger
Chief Financial Officer

**Exhibit 99.01**

**Tonix Pharmaceuticals Announces Data Presentations on TNX-102 SL for Fibromyalgia at the 11th Global Conference on Pharmaceutics and Novel Drug Delivery Systems (PDDS 2024)**

*Presentations highlighted the proprietary formulation technology and pharmacokinetic properties of TNX-102 SL (sublingual cyclobenzaprine HCl)*

*Composition and methods patents based on the eutectic formulation of TNX-102 SL are expected to provide market exclusivity until at least 2034 in the U.S., E.U., Japan, China and other jurisdictions*

*U.S. FDA New Drug Application (NDA) submission on track for October 2024; Fast Track designation granted by FDA; 2025 PDUFA date for FDA decision on approval expected*

*Results from the confirmatory Phase 3 RESILIENT study of TNX-102 SL demonstrated statistically significant improvement in primary endpoint of fibromyalgia nociplastic pain and in all six key secondary endpoints, including sleep quality*

CHATHAM, N.J., September 23, 2024 (GLOBE NEWSWIRE) – Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a fully-integrated biopharmaceutical company with marketed products and a pipeline of development candidates, announced data in two oral presentations and a poster presentation at the 11th Global Conference on Pharmaceutics and Novel Drug Delivery Systems (PDDS 2024), held September 19-21, 2024, in Rome, Italy. Copies of the Company's oral presentations and poster are available under the Scientific Presentations tab of the Tonix website at www.tonixpharma.com following the conference.

Prof. Marino Nebuloni, Director, Qualified Person, Redox Analytical Science Srl, in an oral presentation titled, "*Mannitol as Eutectic Forming Agent for Improved Sublingual Delivery of Cyclobenzaprine HCl,*" described the eutectic formation of cyclobenzaprine HCl and mannitol and how it provides a stable product that dissolves rapidly and delivers cyclobenzaprine by the transmucosal route efficiently into the bloodstream. The eutectic protects cyclobenzaprine HCl from interacting with the basifying agent that is also part of the formulation and required for efficient transmucosal absorption. The work described included studies by Giorgio Reiner and his team at APR Applied Pharma Research S.A. and the team at Tonix.

"Patents based on TNX-102 SL's eutectic composition and its properties have issued in the U.S., E.U., Japan, China and many other jurisdictions around the world," said Seth Lederman, M.D., Chief Executive Officer of Tonix Pharmaceuticals. "The European Patent Office's Opposition Division maintained Tonix's European Patent EP 2 968 992 in unamended form after an Opposition was filed against it by a Sandoz subsidiary, Hexal AG. Hexal AG did not appeal that decision. Tonix had two pre-NDA meetings with the U.S. Food and Drug Administration (FDA) in the second quarter of 2024. The FDA granted TNX-102 SL Fast Track designation in July 2024. The FDA New Drug Application (NDA) submission is on track for October 2024, and a 2025 Prescription Drug User Fee Act (PDUFA) date for an FDA decision on approval is expected."

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Bruce Daugherty, Ph.D., Executive Vice President, Research at Tonix Pharmaceuticals, in the second oral presentation titled, "*Pharmacokinetic Properties of TNX-102 SL, a Sublingual Formulation of Cyclobenzaprine Hydrochloride,*" outlined the clinical pharmacology of TNX-102 SL *via* single dose and multiple dosage administration. The formulation of TNX-102 SL was designed specifically for sublingual administration and transmucosal absorption for bedtime dosing to target disturbed sleep, while reducing the risk of daytime somnolence. Clinical pharmacokinetic studies indicated that the addition of a basifying agent was necessary for efficient transmucosal absorption. The addition of a basifying agent resulted in higher levels of exposure during the first 2 hours after dosing and resulted in deceased levels of the long-lived active metabolite, norcyclobenzaprine in both single dose and multiple dose studies, consistent with bypassing first pass hepatic metabolism. At steady state after 20 days of dosing TNX-102 SL, the dynamic peak level of cyclobenzaprine is higher than the background level of norcyclobenzaprine. In contrast, after 20 days of dosing oral cyclobenzaprine, the simulated peak level of cyclobenzaprine is lower than the simulated background level of norcyclobenzaprine. Tonix believes that TNX-102 SL's dynamic levels of cyclobenzaprine exceeding norcyclobenzaprine levels after steady state modeling of chronic dosing, contributes to the durability of its clinical benefits. Dr. Daugherty also presented evidence showing that cyclobenzaprine interacts as an antagonist at four different receptors in the brain, which are believed to play roles in sleep quality supporting the multi-functional mechanism of TNX-102 SL. The presentation also illustrated the prevalence of fibromyalgia and the unmet need for new treatments in the U.S., despite the availability of three FDA-approved drugs. In the Phase 3 RESILIENT study in fibromyalgia, TNX-102 SL met the pre-specified primary endpoint of significantly reducing daily pain as compared to placebo (p-value=0.00005). TNX-102 SL also demonstrated broad syndromal benefits with statistically significant improvement in all six pre-specified key secondary endpoints including those related to improving sleep quality, reducing fatigue, and improving patient global ratings and overall fibromyalgia symptoms and function. TNX-102 SL was well tolerated with an adverse event profile comparable to prior studies and no new safety signals were observed.

Dr. Lederman continued, "There remains a significant unmet need in fibromyalgia for an effective treatment given the frustrations with existing therapeutic options. TNX-102 SL has demonstrated it has the potential to provide broad-spectrum symptom relief in fibromyalgia as a once-daily treatment at bedtime. With the support of statistically significant results from two Phase 3 studies of TNX-102 SL in fibromyalgia, TNX-102 SL is potentially positioned to be the first new treatment option for fibromyalgia patients in 15 years."

Siobhan Fogarty, Executive Vice President, Product Development at Tonix Pharmaceuticals, in the poster presentation titled, "*The Importance of In Vitro Discriminatory Tests in the Development of a Sublingual Dosage Form of TNX-102 SL (Cyclobenzaprine HCl) Tablets,*" presented the development of *in vitro* techniques used to assess characteristics of the TNX-102 SL tablet including dissolution, "disintegration time" and a proprietary "wetting time" test. These *in vitro* tests assessed the impact of the particle size, excipient variation and compression force. The data presented indicate that a dissolution test does not discriminate between tablets made with intentional modifications to particle size, excipient content or compression strength. However, both "disintegration time" and "wetting time" are sensitive tests to discriminate differences in particle size, concentration of the excipient Pearlitol Flash and compression strength.

Dr. Lederman concluded, "The *in vitro* "disintegration time" and "wetting time" tests have supported an efficient clinical development process and provide a strategy to evaluate manufacturing processes and product uniformity going forward. The *in vitro* discriminatory tests have been utilized by Tonix in the scale-up, validation and launch preparation of TNX-102 SL at the contract drug manufacturing organization sites. Together, these data suggest that TNX-102 SL has the potential to address a significant unmet need for fibromyalgia patients."

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**About Redox - Analytical Science Srl**

Redox is an independent CRO company headquartered in Monza, Italy with research and development activities and customer analytical support to pharmaceutical companies for more than 30 years. For more than 25 years the analytical activities have been certified by national and international agencies (European Medicines Agency, the Italian Medicines Agency (AIFA), FDA, etc. One of its main activities is the development of new drug products in order to improve the pharmaceutical actions, in concert with improvement in the stability and reduction of the cost of the new drug substances. Several unique and sophisticated analytical techniques and equipment are used in support of these research and development strategies, focused on achieving optimal and effective pharmaceutical formulation in the shortest time frame. More than 30 professional people are dedicated to Redox's efforts and many of its projects are ongoing in collaboration with the pharmaceutical industry as well as with Italian and international universities.

Further information about Redox can be found at www.labredox.com.

**About APR Applied Pharma Research S.A., a wholly-owned subsidiary of Relief Therapeutics Holding AG**

APR Applied Pharma Research S.A., a wholly-owned subsidiary of Relief Therapeutics Holding AG, is a commercial-stage biopharmaceutical company committed to advancing treatment paradigms and delivering improvements in efficacy, safety, and convenience to benefit the lives of patients living with select specialty and rare diseases. Relief Therapeutics' portfolio offers a balanced mix of marketed, revenue-generating products, including the proprietary, globally patented Physiomimic™ and TEHCLO™ platform technologies and a targeted clinical development pipeline consisting of risk-mitigated assets focused in three core therapeutic areas: rare metabolic disorders, rare skin diseases and rare respiratory diseases. In addition, Relief Therapeutics is commercializing several legacy products via licensing and distribution partners. Relief Therapeutics' mission is to provide therapeutic relief to those suffering from rare diseases and is being advanced by an international team of well-established, experienced biopharma industry leaders with extensive research, development and rare disease expertise. Relief Therapeutics is headquartered in Geneva, with additional offices in Balerna, Switzerland, Offenbach am Main, Germany and Monza, Italy. Relief Therapeutics is listed on the SIX Swiss Exchange under the symbol RLF.

Further information about APR can be found at www.relieftherapeutics.com or by following Relief Therapeutics on LinkedIn and Twitter.

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**Tonix Pharmaceuticals Holding Corp.***

Tonix is a fully-integrated biopharmaceutical company focused on developing, licensing and commercializing therapeutics to treat and prevent human disease and alleviate suffering. Tonix's priority is to submit a New Drug Application (NDA) to the FDA in October of 2024 for TNX-102 SL, a product candidate for which two statistically significant Phase 3 studies have been completed for the management of fibromyalgia. The FDA has granted Fast Track designation to TNX-102 SL for the management of fibromyalgia. TNX-102 SL is also being developed to treat acute stress reaction. Tonix recently announced the U.S. Department of Defense (DoD), Defense Threat Reduction Agency (DTRA) awarded it a contract for up to $34 million over five years in an Other Transaction Agreement (OTA) to develop TNX-4200 small molecule broad-spectrum antiviral agents targeting CD45 for the prevention or treatment of infections to improve the medical readiness of military personnel in biological threat environments. Tonix owns and operates a state-of-the art infectious disease research facility in Frederick, MD. The company's Good Manufacturing Practice (GMP)-capable advanced manufacturing facility in Dartmouth, MA was purpose-built to manufacture TNX-801 (live horsepox vaccine) for the prevention of mpox and other vaccines on the horsepox platform. The GMP suites are ready to be reactivated in case of a national or international emergency. Tonix's development portfolio is focused on central nervous system (CNS) disorders. Tonix's CNS portfolio includes TNX-1300 (cocaine esterase), a biologic in Phase 2 development designed to treat cocaine intoxication that has Breakthrough Therapy designation. Tonix's immunology development portfolio consists of biologics to address organ transplant rejection, autoimmunity and cancer, including TNX-1500, which is a humanized monoclonal antibody targeting CD40-ligand (CD40L or CD154) being developed for the prevention of allograft rejection and for the treatment of autoimmune diseases. Tonix also has product candidates in development in the areas of rare disease and infectious disease. Tonix Medicines, our commercial subsidiary, markets Zembrace® SymTouch® (sumatriptan injection) 3 mg and Tosymra® (sumatriptan nasal spray) 10 mg for the treatment of acute migraine with or without aura in adults.

*Tonix's product development candidates are investigational new drugs or biologics and have not been approved for any indication.

Zembrace SymTouch and Tosymra are registered trademarks of Tonix Medicines. All other marks are property of their respective owners.

This press release and further information about Tonix can be found atwww.tonixpharma.com.

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**Forward Looking Statements**

Certain statements in this press release are forward-looking within the meaning of the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as "anticipate," "believe," "forecast," "estimate," "expect," and "intend," among others. These forward-looking statements are based on Tonix's current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, risks related to the failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; risks related to the failure to successfully market any of our products; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. Tonix does not undertake an obligation to update or revise any forward-looking statement. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2023, as filed with the Securities and Exchange Commission (the "SEC") on April 1, 2024, and periodic reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements. The information set forth herein speaks only as of the date thereof.

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**Exhibit 99.02**

# Mannitol as a eutectic forming agent for improved sublingual delivery of Cyclobenzapine HCl

Prof. Marino Nebuloni



11th Global Conference on Pharmaceutics and Novel Drug Delivery Systems (PDDS), Rome September 19, 2024. Oral Presentation.

## Disclosures

- Prof. Nebuloni is an employee of Redox Analytical Science Srl
- Research funded by Tonix Pharmaceuticals, Inc.

# Content

- Drug-excipient compatibility strategy
- Eutectic solid state complex formation : benefit on dissolution profile and physical and chemical stability
- Case study: Cyclobenzaprine HCl - excipient compatibility for sublingual drug product formulation
- D-mannitol polymorphism influence on eutectic formation
- Investigation by suitable techniques - *thermal analysis, X-ray spectroscopy, Intrinsic Dissolution Rate, Scanning Electron Microscopy, $C^{13}$ NMR at solid state, etc.*
- Characterization and pharmaceutical influence of eutectic in pharmaceutical properties *-stability, dissolution, particle morphology and machinability on sublingual tablet formulation-*
- Influence of basic excipient present in the drug product.
- Conclusion



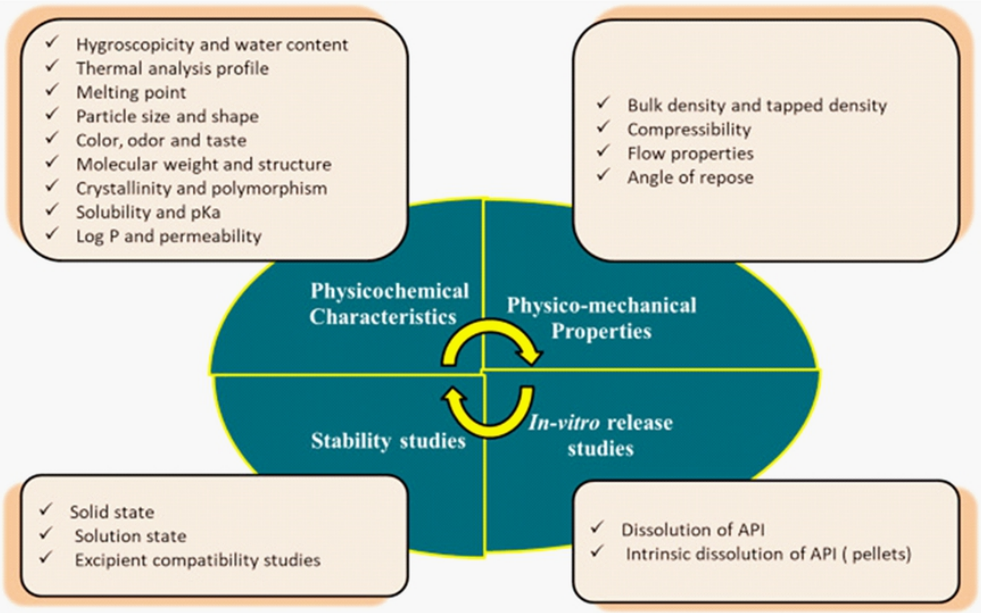


# Compatibility strategy

## excipient impact

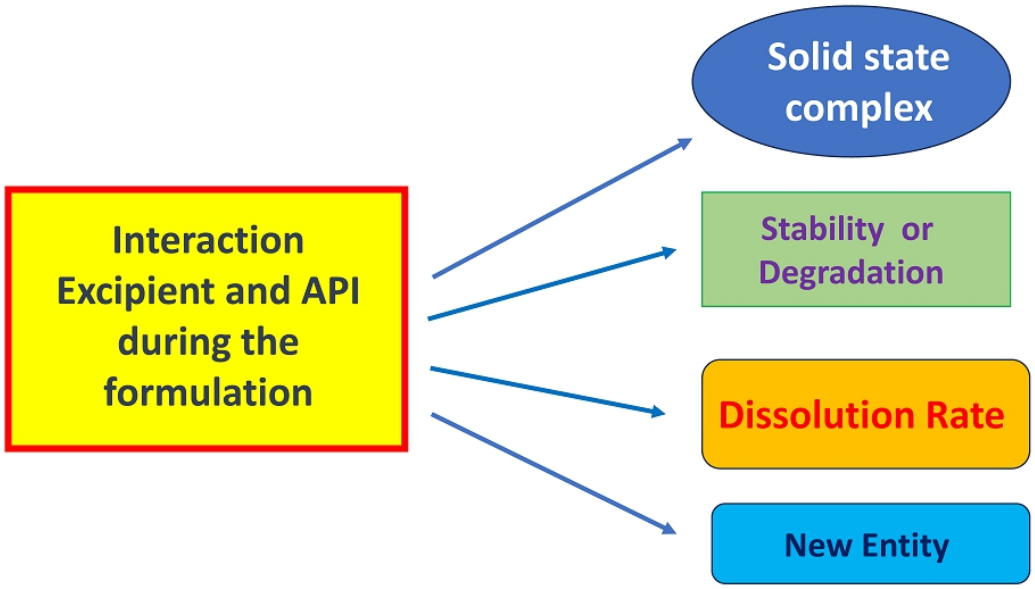
- ***Pharmaceutical excipients have important functions such as serving as carriers, improving drug stability, solubilization and increasing or slowing down the drug release.***
- ***The laws and regulatory agencies have made rigid regulations on the compatibility of APIs and excipients of various dosage forms.***
- ***Pharmaceutical Development Q8 (R2) – ICH. Chapter "2.1.1" points out that a compatibility test of APIs and excipients is required at the beginning of formulation development***
- ***The early prediction of drug-excipient incompatibility is vital in the pharmaceutical industry to avoid costly material wastage and time delays***

# Thermodynamic paramiters in API-Excipient interaction






# Main Interaction and Physico-chemical Impact on API



# Drug Excipient Compatibility -Experimental Design-

- ***Before initiating drug product development, the formulation scientist must fully consider the chemical structure of the API and the type of delivering system***
- ***Initial selection of excipients should be based on appropriate delivery characterisation.***
- ***Potential mechanism of degradation of the drug.***
- ***Know chemical incompatibility reported in published information***

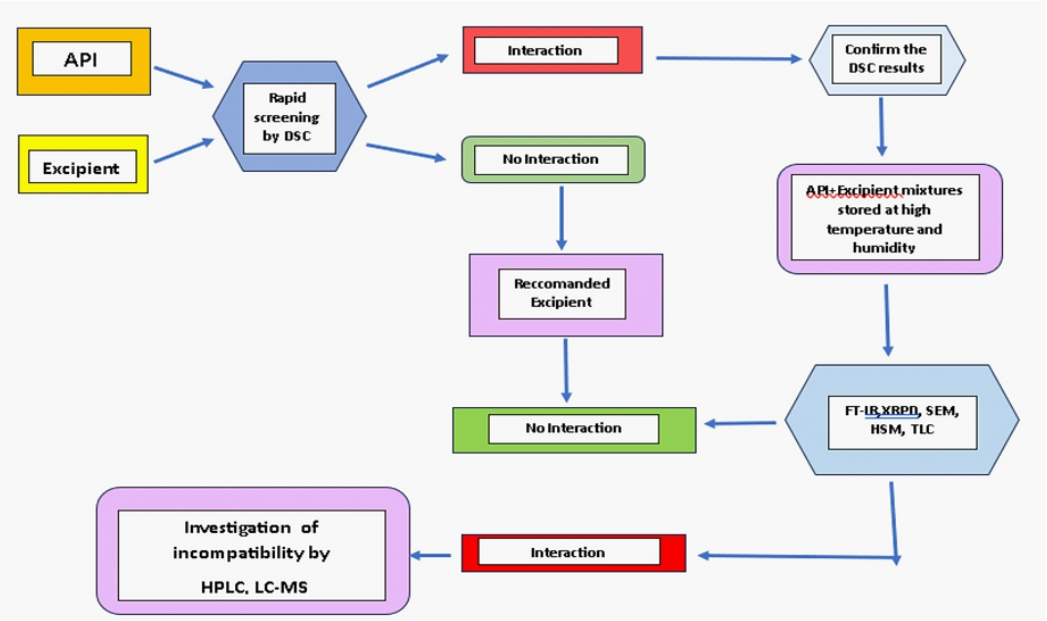




# Analytical Methods for drug-excipient compatibility assessment

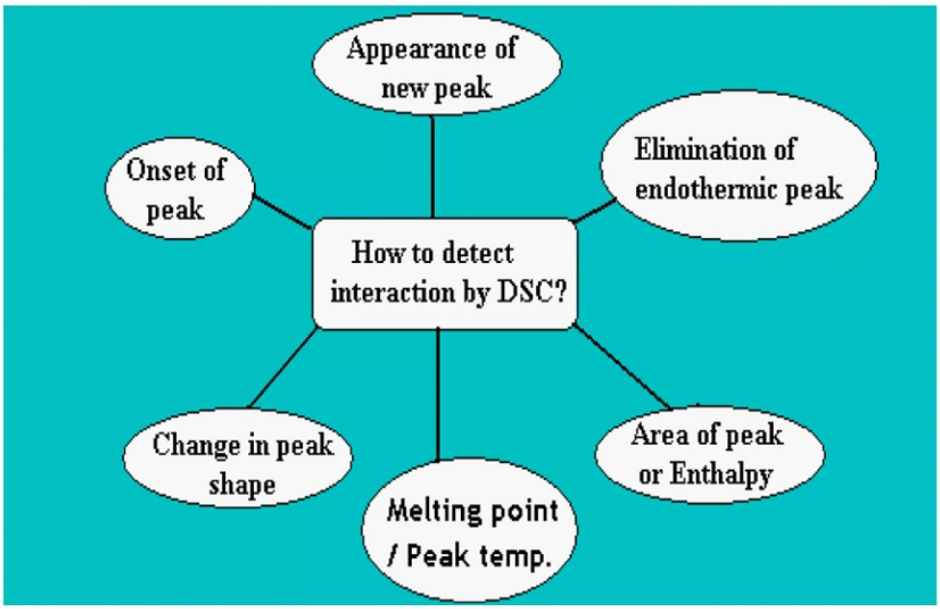
- ***Thermal Methods (DSC, TGA, Hot Stage Micros.)***
- ***FT-IR Spectroscopy***
- ***X-Ray Powder Diffraction***
- ***Scanning Electron Microscopy (SEM)***
- ***Dissolution Rate profile & Intrinsic Dissolution Rate***
- ***NMR at the solid state***

# Drug–excipient compatibility screening—Role of thermoanalytical and spectroscopic techniques



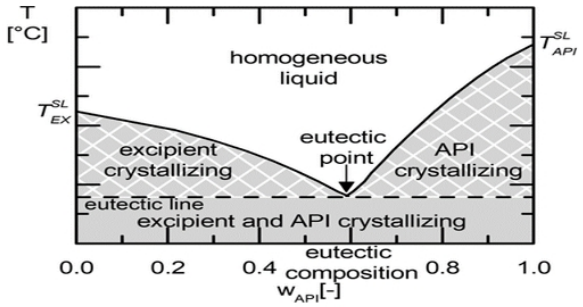



# Investigation by Thermal Analysis (DSC)



# Eutectic formation during interaction

An eutectic is defined as a mixture of two or more compounds that are typically solid at room temperature, but when combined at a particular molar ratio, presents a significant melting point depression




The eutectic formation in several cases can improve the cohesion between the particles and assure better physical bounding between the drug substance and the excipient. Nevertheless, the physical state prevents the erosion of the final dosage form.





## *Case Study:* compatibility investigation in sublingual formulation

## *TNX-102 SL (Cyclobenzaprine HCl Sublingual Tablets)*[1]

**Tonix**

Pharmaceuticals

## *Activity*

**Fibromyalgia, Long COVID, Acute Stress Disorder……**



[1]TNX-102 SL is an experimental new drug and has not been approved for any indication

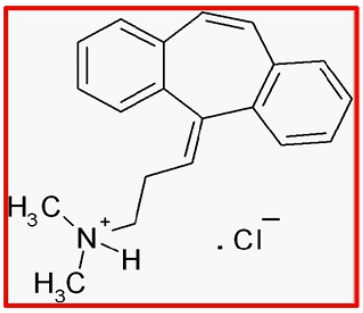
# Formulation development of TNX-102 SL tablet
## - trial n°1 -

| Component | Studied Formulation (mg) |
|---|---|
| Cyclobenzaprine HCl | 2.8 |
| D-mannitol | 2.5 |
| Perlitol Flash (D-mannitol:corn starch) | 28.0 |
| Crospovidone | 2.0 |
| Sodium Stearyl Fumarate | 1.2 |
| Colloidal silicon dioxide | 1.0 |
| Dibasic potassium phosphate | 0.5 |
| *Total Theoretical Tablet Weight* | **38** |

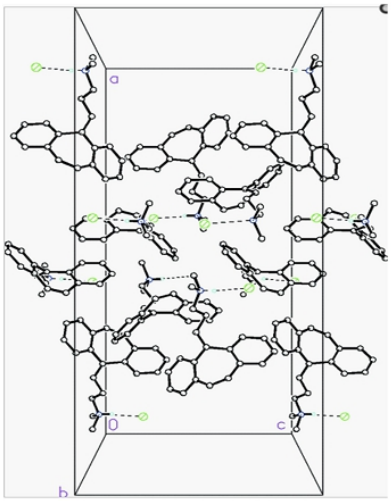




# Crystal Structure of Cyclobenzaprine.HCl

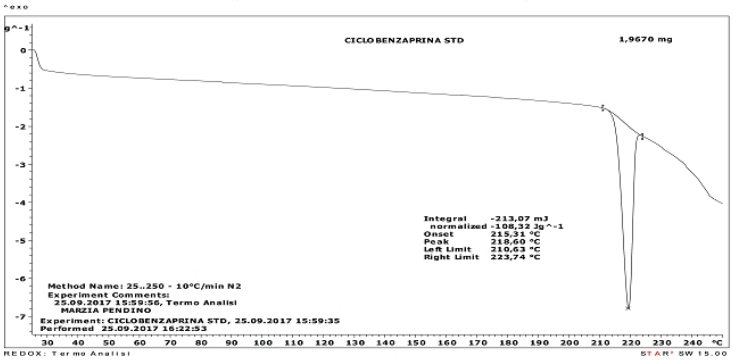



**Cyclobenzaprine is a tricyclic approved in the U.S. for short-term use as a muscle relaxant. It works by blocking nerve impulses (or pain sensations) in the brain.**



**M.S. Siddegowda**
Acta Crystallogr Sect E Struct Rep Online. 2011 July 1; 67(Pt 7):

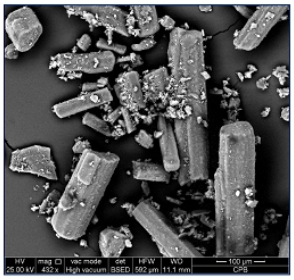
# Physical Properties of Cyclobenzaprine HCl



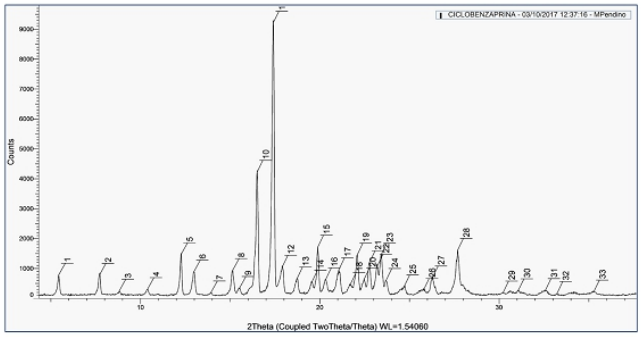

**DSC**

**mp: 215.3 °C**

**SEM**



**XRPD**

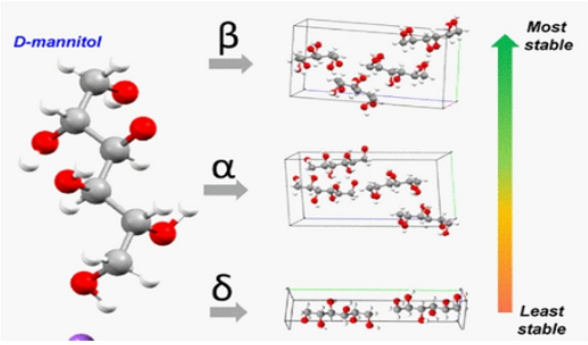




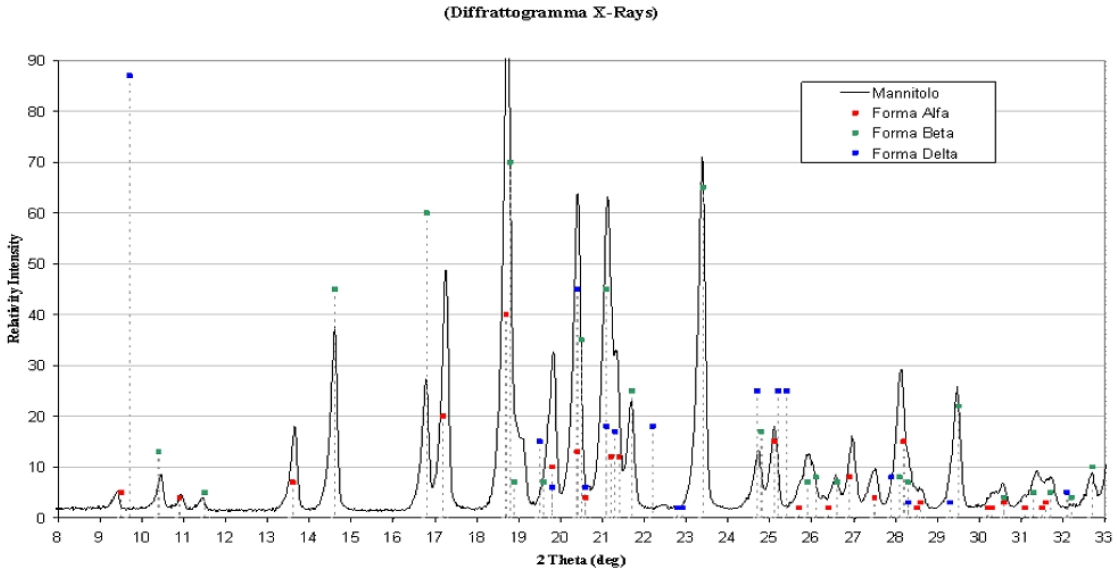

# D-mannitol Poymorphic Forms

| Polymorphic Form | Melting point (°C) | Heat of melting (kJ/mole) | Crystal system | XRPD peak position (2θ) |
|---|---|---|---|---|
| α alfa | 166 | 52 | orthorombic | 13.6° - 17.2° |
| β beta | 166.4 | 53 | orthorombic | 10.4°- 14.6°- 23.4° |
| δ delta | 154 | | monoclinic | 9.7°- 22.2° |

**Thermal Stability**



# D-mannitol –X ray comparison between the polymorphic forms








# D-mannitol crystallization and polymorphic transition

Metastable phase nucleation

Delta Form

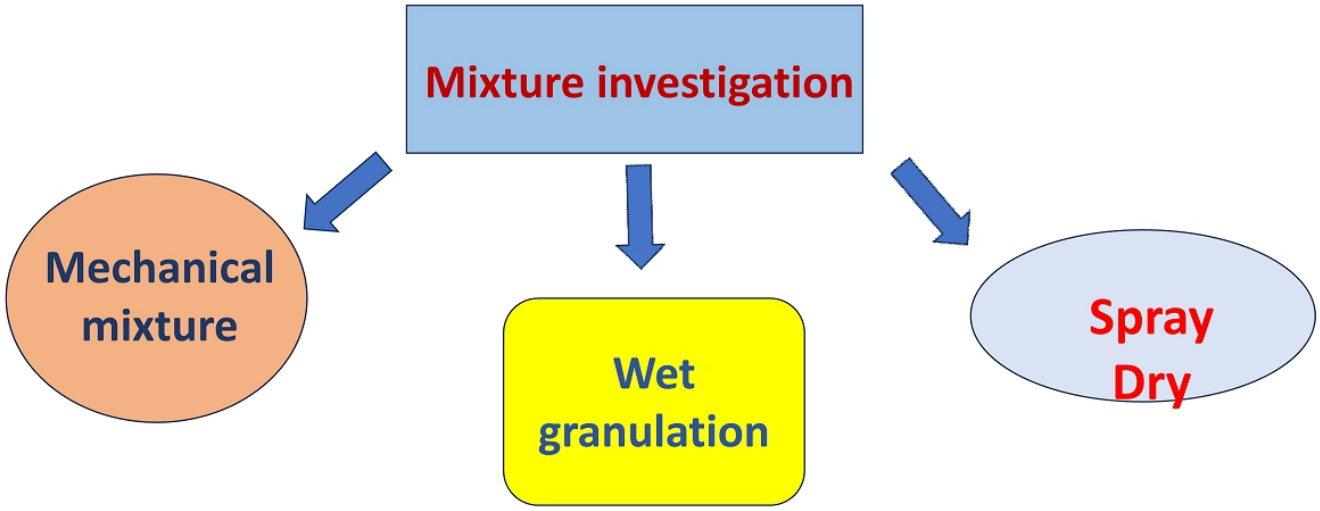
Delta to Beta

Metastable + Delta + Beta

Crystalline Beta Form

***Optical microscopy polarized light***

# Compatibility procedure
## CBP HCl + Excipients

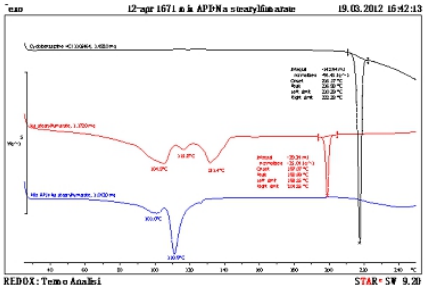




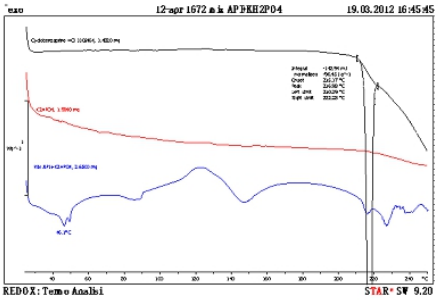



# DSC Compatibility Results
## -mechanical mixtures -

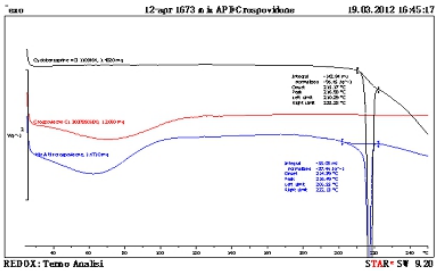
CBP HCl lubricant



CBP HCl $K_2HPO_4$

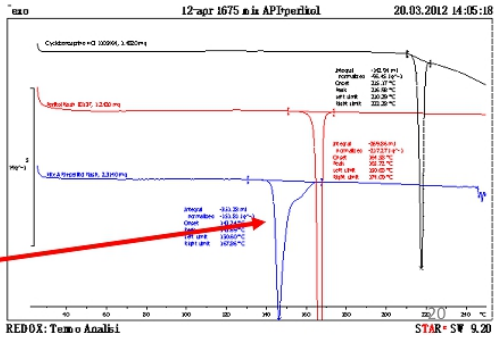


CBP HCl Crospov.



CBP HCl Mannitol beta

Eutectic



# Results of Compatibility Screening Cyclobenzaprine HCl with each excipient by DSC

| Excipient | Mixture with CBP HCl (1:1) | Formulation ratio |
|---|---|---|
| lubricant | NO | NO |
| D mannitol (beta form) | Eutectic formation | Eutectic formation |
| Sicon Colloidal | NO | NO |
| Crospovidone | NO | NO |
| Potassium bibasic phosphate | Acid base interaction | Acid base interaction |
| Perlitol Flash 200 (D mannitol) | Eutectic formation | Eutectic formation |
| ..... | ..... | ..... |



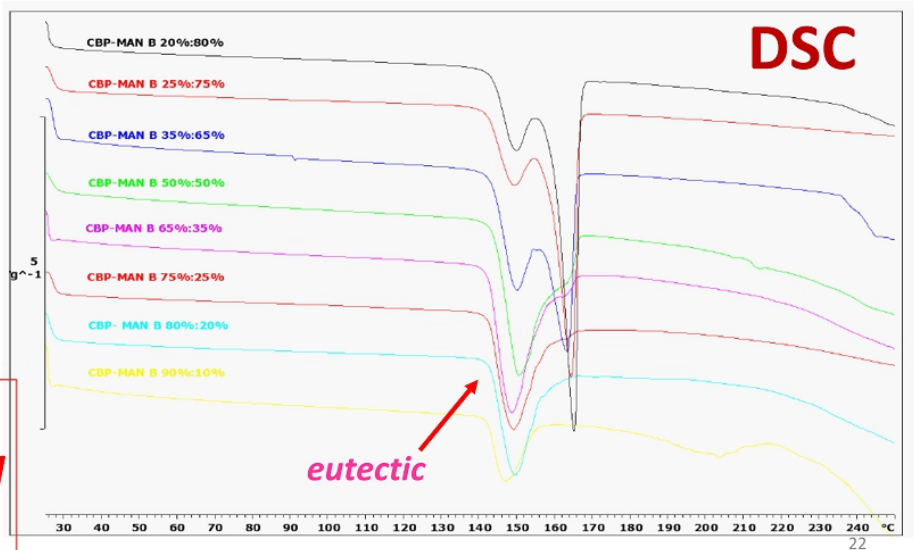


# Eutectic formation between Cyclobenzaprine HCl and D-mannitol - beta form -

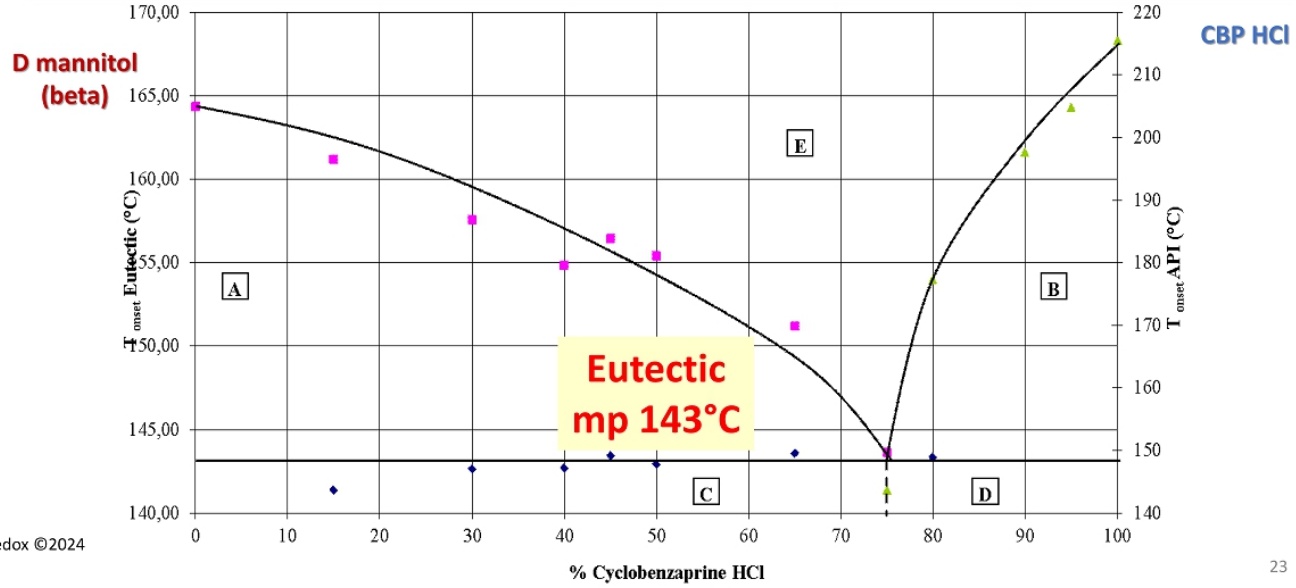
## Ratio

| CBP HCl | D mannitol (beta form) |
|---|---|
| 20 | 80 |
| 25 | 75 |
| 35 | 65 |
| 50 | 50 |
| 65 | 35 |
| 80 | 20 |
| 90 | 10 |

***Eutectic ratio CBP HCl : D-mannitol (75:25)***



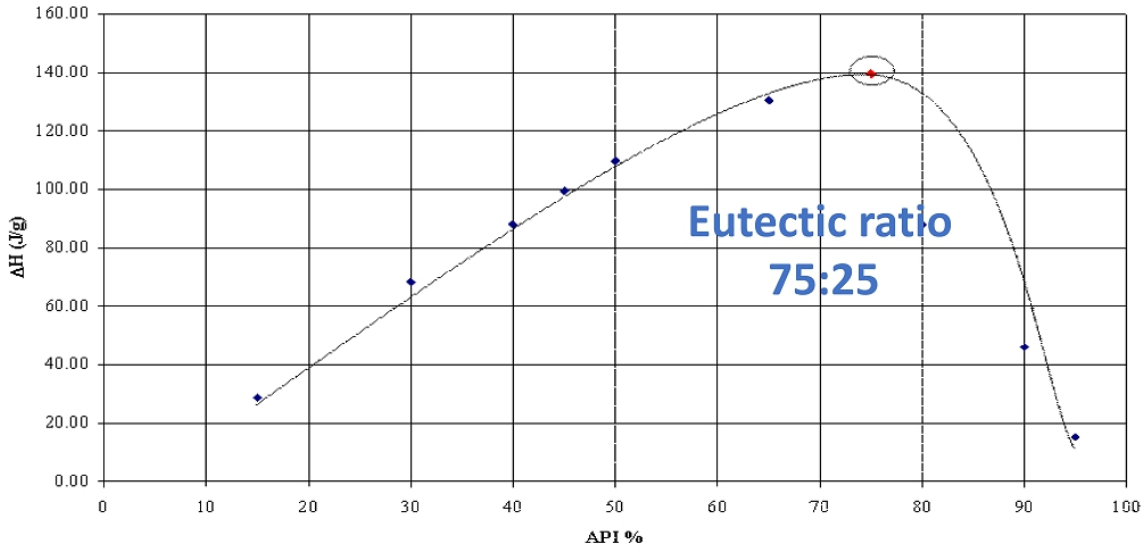
# Phase Diagram
# Cyclobenzaprine HCl – D-mannitol (beta form)



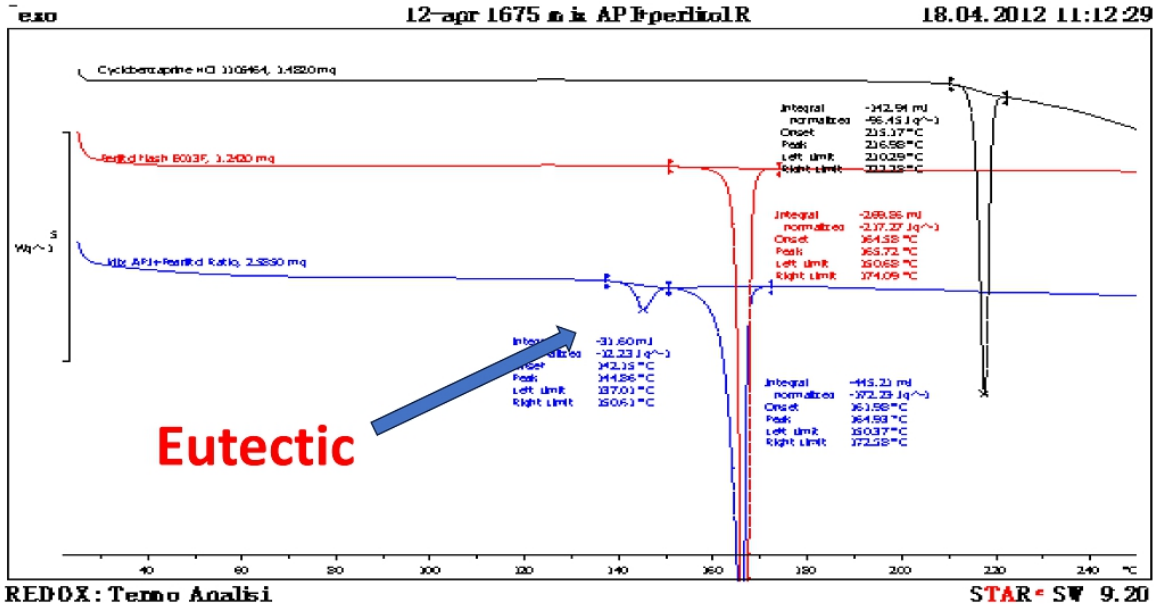





# Phase Diagram by Melting Enthalpy of the Eutectic



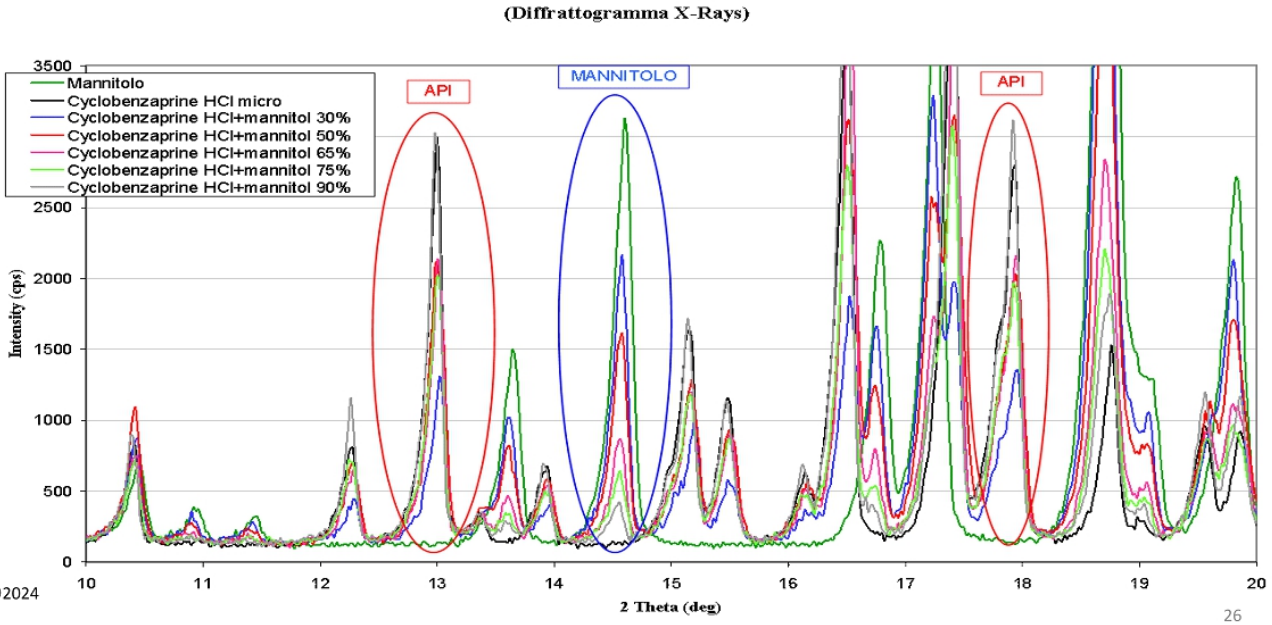
# Eutectic present in the formulation



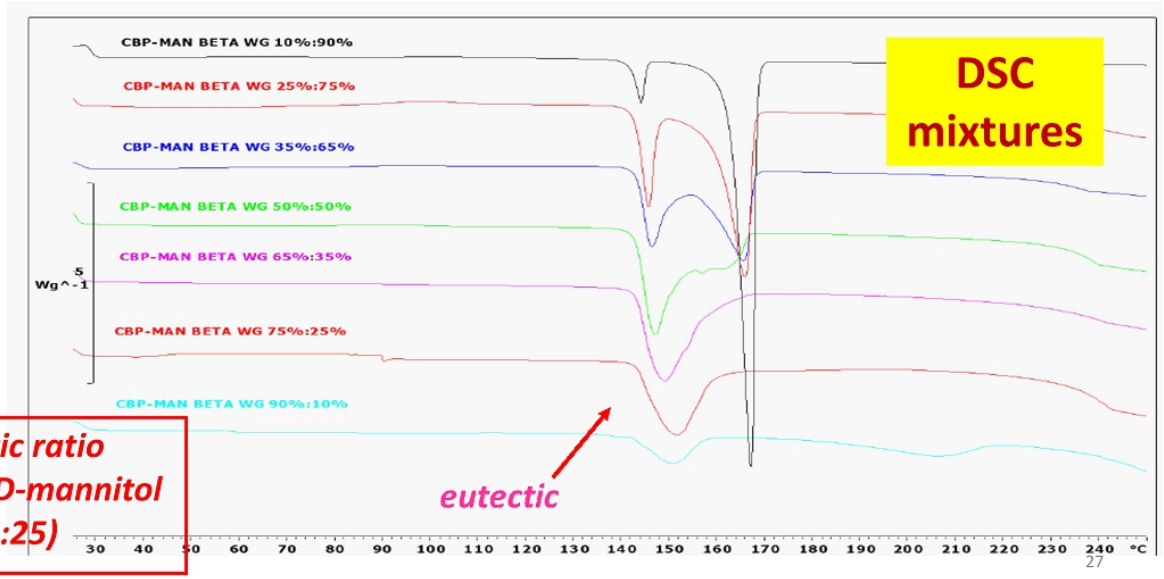



# XRPD of CBP HCl:D-mannitol mixtures

## - no chemical interaction with new entity formation -



# Compatibility by Wet Granulation
## CBP HCl – D-mannitol (beta)




***Eutectic ratio CBP HCl : D-mannitol (75:25)***

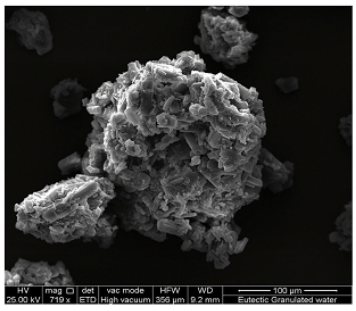


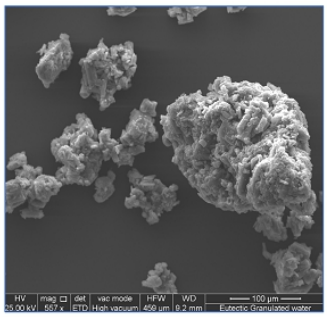


# Eutectic Morphology by SEM of the mixtures

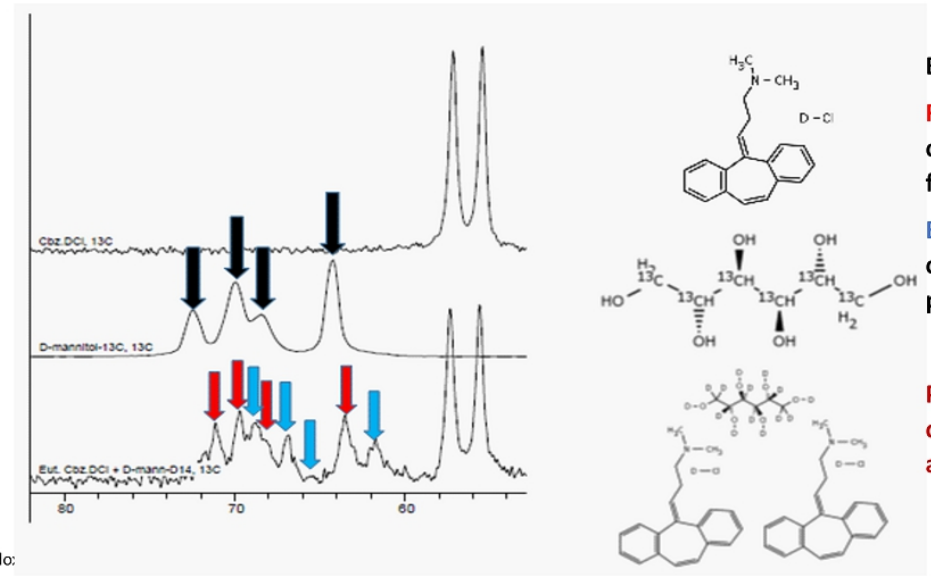
***mechanical***

***wet granulation***





# $C_{13}$ NMR on D-mannitol alone and D-mannitol in eutectic with Cyclobenzaprine HCl




**Black:** D-mannitol alone (beta form)

**Red:** D-mannitol in eutectic: major component (shifted upfield ~ 1 ppm from D-mannitol alone)

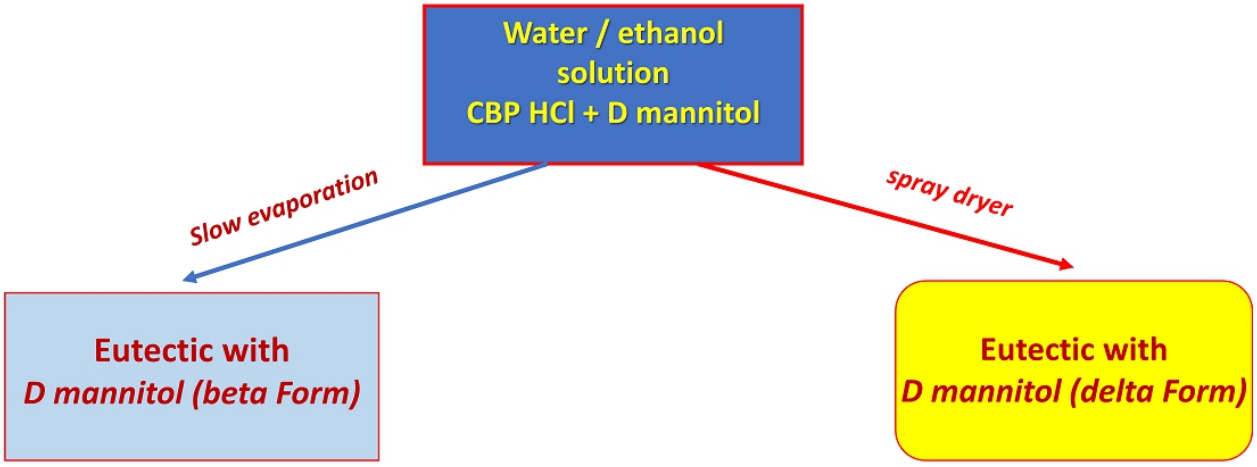
**Blue:** D-mannitol in eutectic: minor component (shifted upfield ~ 2.8 ppm from D-mannitol alone)

**Peaks in 50-60ppm region, from cyclobenzaprine HCl, are not affected in the eutectic.**

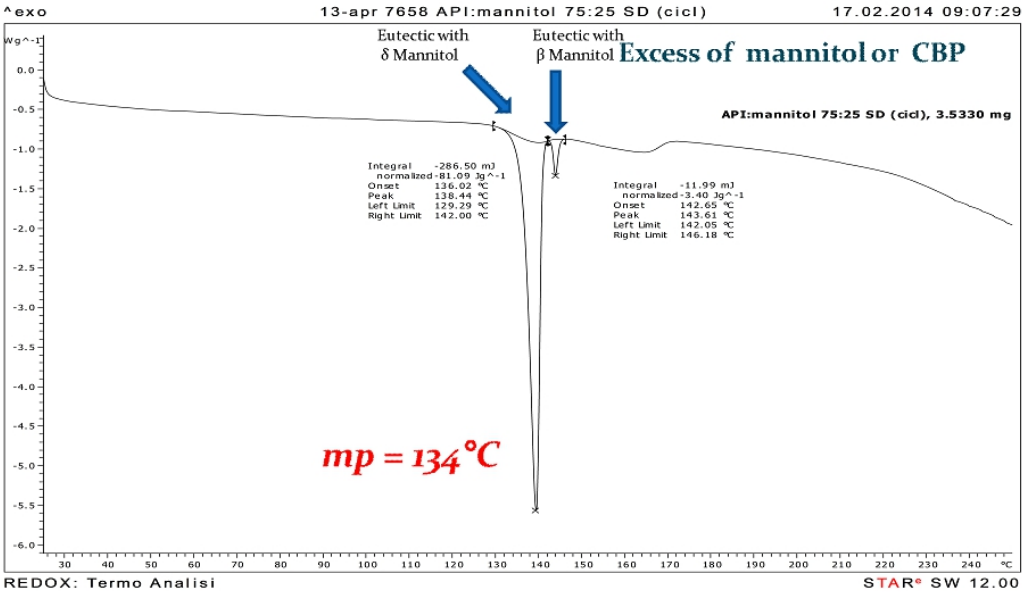
Redo:



# Screening by spray dry process to reduce the eutectic particle size and improve the dissolution rate

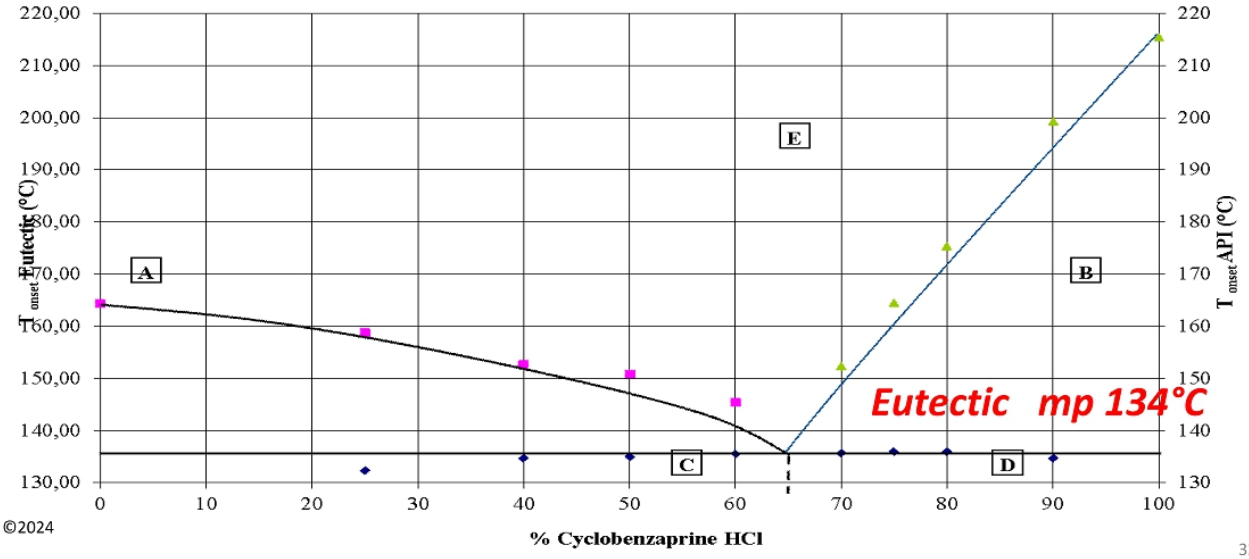


# Cyclobenzaprine HCl : D mannitol *delta form* (eutectic - ratio 65:35)

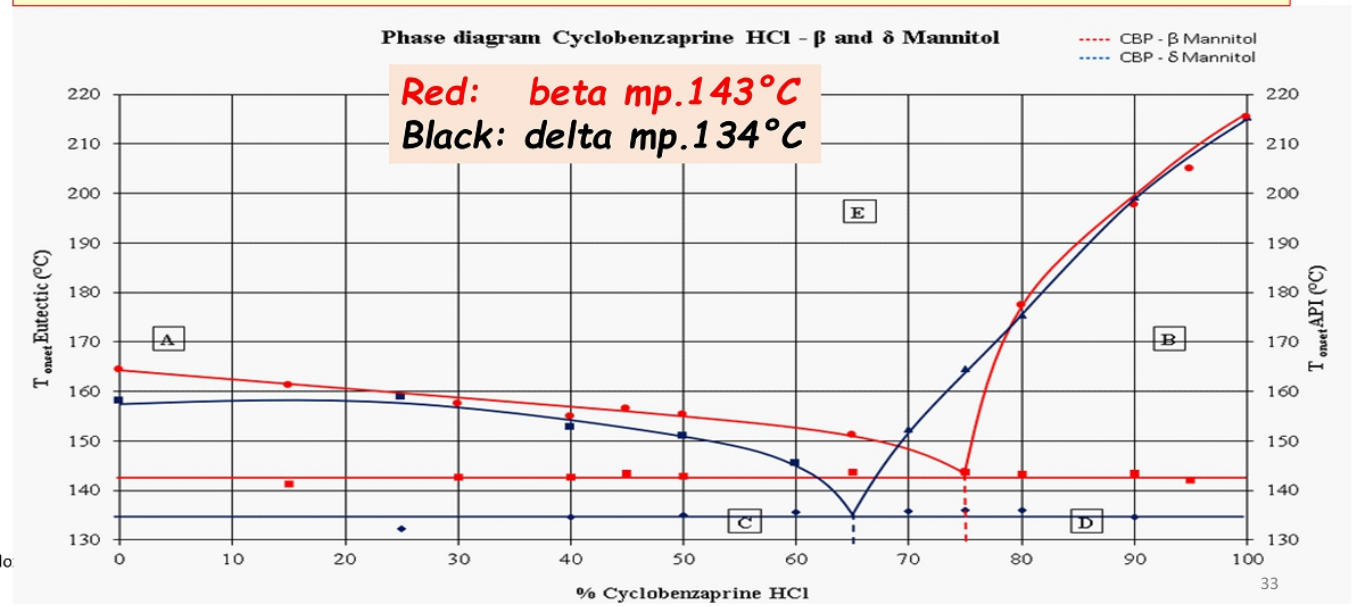





# Phase Diagram
# Cyclobenzaprine HCl : D-mannitol (*delta form*)



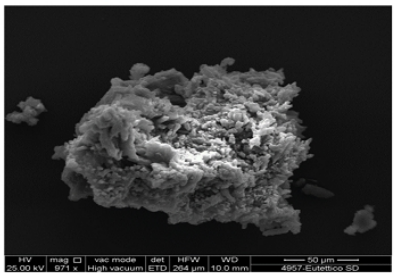
# Comparison of Phase Diagrams
## Cyclobenzaprine HCl – D mannitol (beta vs. delta)

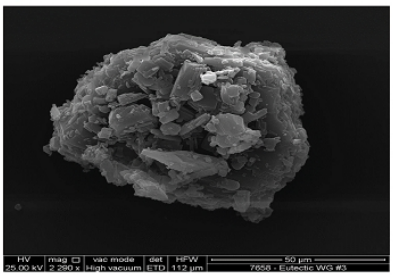




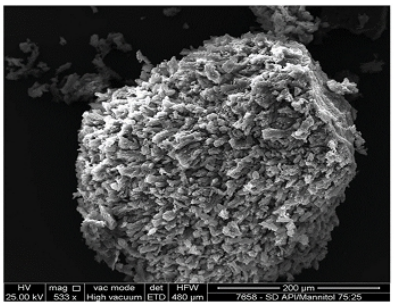

# Morphology of Eutectics by SEM (beta vs delta)

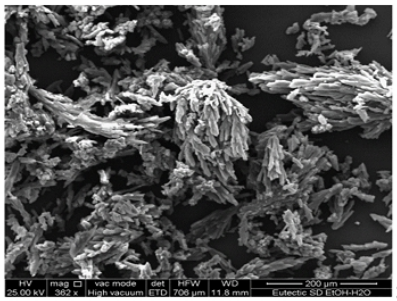
wet granulation
*D mannitol Beta form*



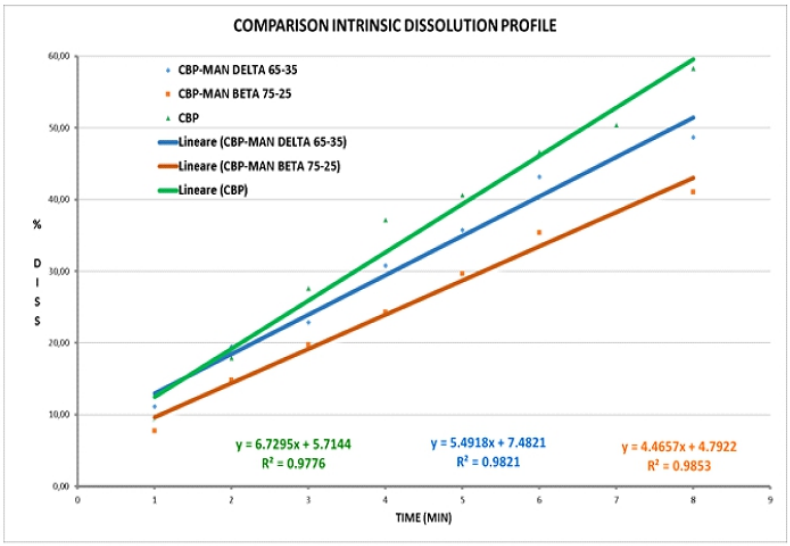


*spray dry*
*D mannitol delta form*





# Intrinsic Dissolution Rate (IDR)




**Medium Composition**

- Water
- Methocel 0.3%
- Pyrophosphoric ac. 0.5%
- pH: 4.5

- Weight 120 mg
- Pressure 10 Kpsi
- Surface 0.5 $cm_2$
- Rotation 50 rpm
- Temp. 37 °C
- UV-vis 224 nm

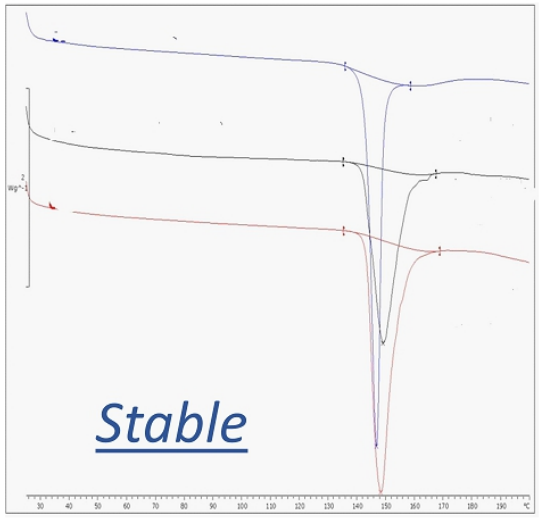
| Sample | I.D.R. (%/min) | $R^2$ |
|---|---|---|
| Cyclobenzaprine HCl | 6.73 | 0.97 |
| Eutectic mixture Beta mannitol (75:25) | 4.47 | 0.98 |
| Eutectic mixture Delta mannitol (65:35) | 5.50 | 0.98 |



**Eutectic with Delta Form is 23% more rapid in dissolution than beta one**



# Stability on the time of the two Eutectics

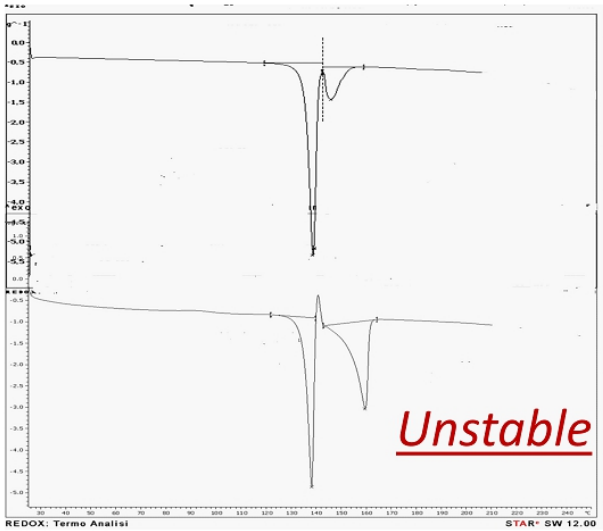



*time*

To

$T_6$ months

$T_{12}$ months



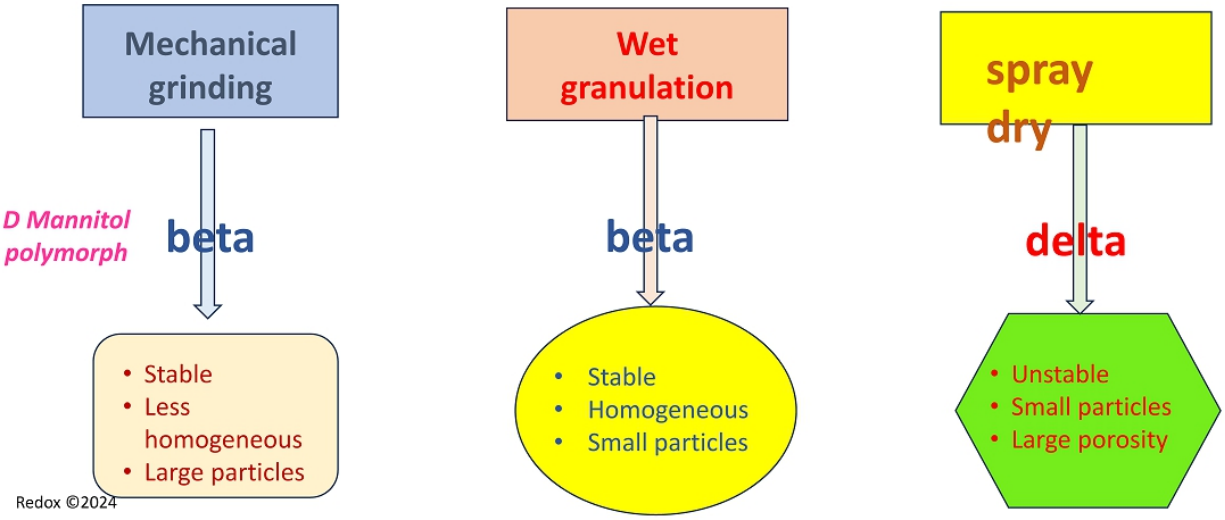

Eutectic CBP HCl : D-mannitol (75:25)

***beta Form***

Eutectic CBP HCl : D-mannitol (65:35)

***delta Form***

# Eutectic stability in relation to the process





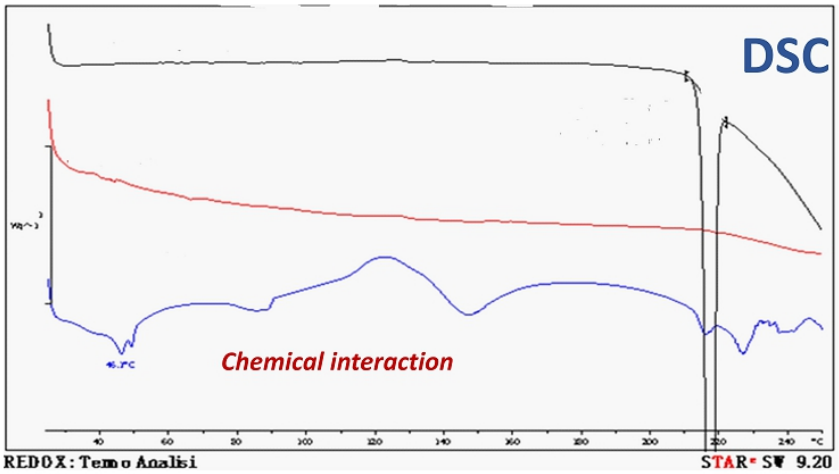

# Interaction of the eutectic with Dipotasium phosphate ($K_2HPO_4$)

*The Screening Compatibility test shows degradation of the CBP HCl with possible free base formation ( CBP HCl+$K_2HPO_4$ →CBP + KCl + H2O+Phosphates)*

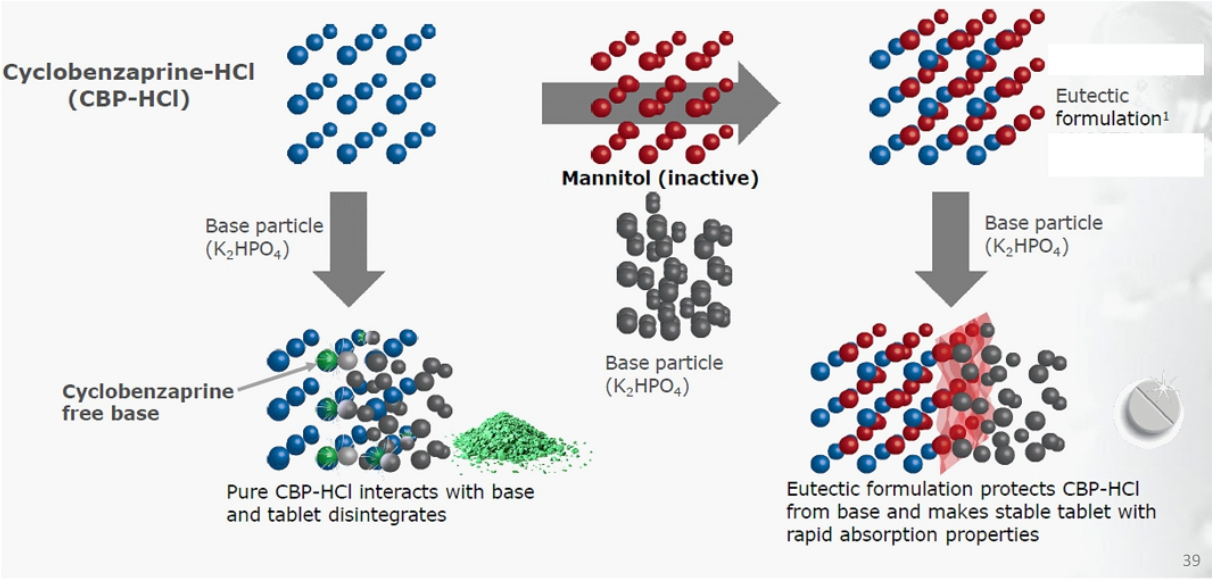
***Cyclobenzaprine HCl***

**$K_2HPO_4$**

**Mix (1:1)**
**CBP HCl + $K_2HPO_4$**



# Proprietary Cyclobenzaprine HCl Eutectic stabilizes Transmucosal Sublingual Tablet Formulation






# Influence of mouth pH on SL tablet dissolution and cyclobenzaprine free base formation

***Free particle contact between CBP.HCl with $K_2HPO_4$***

***No Compatibility rapid free CBP base formation***

***DEGRADATION***

**Oral cavity pH = 6.6-7.5**

**Eutectic**

***Rapid dissolution Fast transmucosal permeability***

***STABLE***



**Cyclobenzaprine HCl pKa= 9.7**
**Dipotassium phosphate pKa = 12.4**

# Advantage of the Eutectic formation as a powerful Drug Delivery System

The knowledge of drug-excipient compatibility is vital in the pharmaceutical industry to avoid costly material wastage and time delays

**Tablet SL**

- Stability of CBP HCl
- Protection from basic excipient
- Fast Dissolution Rate
- Low hygroscopicity
- .....

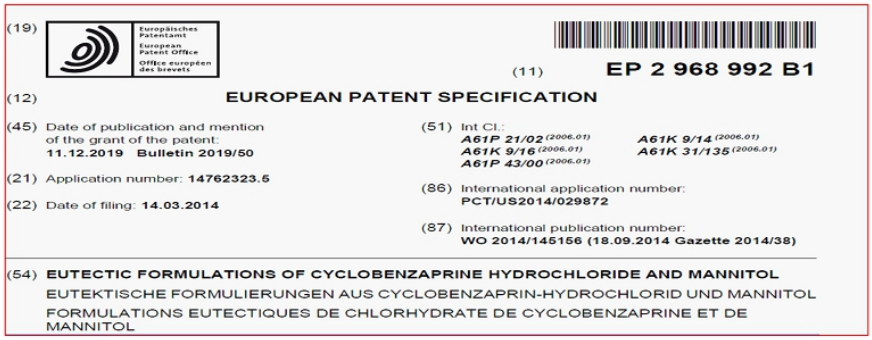

**ACTIVE**

- *Fast transmucosal permeability*
- *Reduce CBP HCl amount of dose*
- *Balances between efficacy and tolerability.*





# Patents related to eutectic CBP HCl + D mannitol



(19) Europäisches Patentamt / European Patent Office / Office européen des brevets

(11) EP 2 968 992 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent: 11.12.2019 Bulletin 2019/50

(21) Application number: 14762323.5

(22) Date of filing: 14.03.2014

(51) Int Cl.: A61P 21/02 (2006.01) A61K 9/14 (2006.01) A61K 9/16 (2006.01) A61K 31/135 (2006.01) A61P 43/00 (2006.01)

(86) International application number: PCT/US2014/029872

(87) International publication number: WO 2014/145156 (18.09.2014 Gazette 2014/38)

(54) EUTECTIC FORMULATIONS OF CYCLOBENZAPRINE HYDROCHLORIDE AND MANNITOL

EUTEKTISCHE FORMULIERUNGEN AUS CYCLOBENZAPRIN-HYDROCHLORID UND MANNITOL

FORMULATIONS EUTECTIQUES DE CHLORHYDRATE DE CYCLOBENZAPRINE ET DE MANNITOL

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau

(43) International Publication Date 18 September 2014 (18.09.2014)

WIPO | PCT

(10) International Publication Number WO 2014/145156 A2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau

(43) International Publication Date 24 March 2016 (24.03.2016)

WIPO | PCT

(10) International Publication Number WO 2016/044796 A1

some others

- The United States Patent and Trademark Office (USPTO) issued United States Patent No. 9636408 in May 2017,
- Patent No. 9956188 in May 2018,
- Patent No. 10117936 in November 2018,
- Patent No. 10,357,465 in July 2019,

# Example of Benefits from closely working together

**Research**

REDOX
Analytical Chemistry & Process Safety Testing
Viale G.B. Stucchi 62/26 Monza

**Development**

APR
A Relief Company

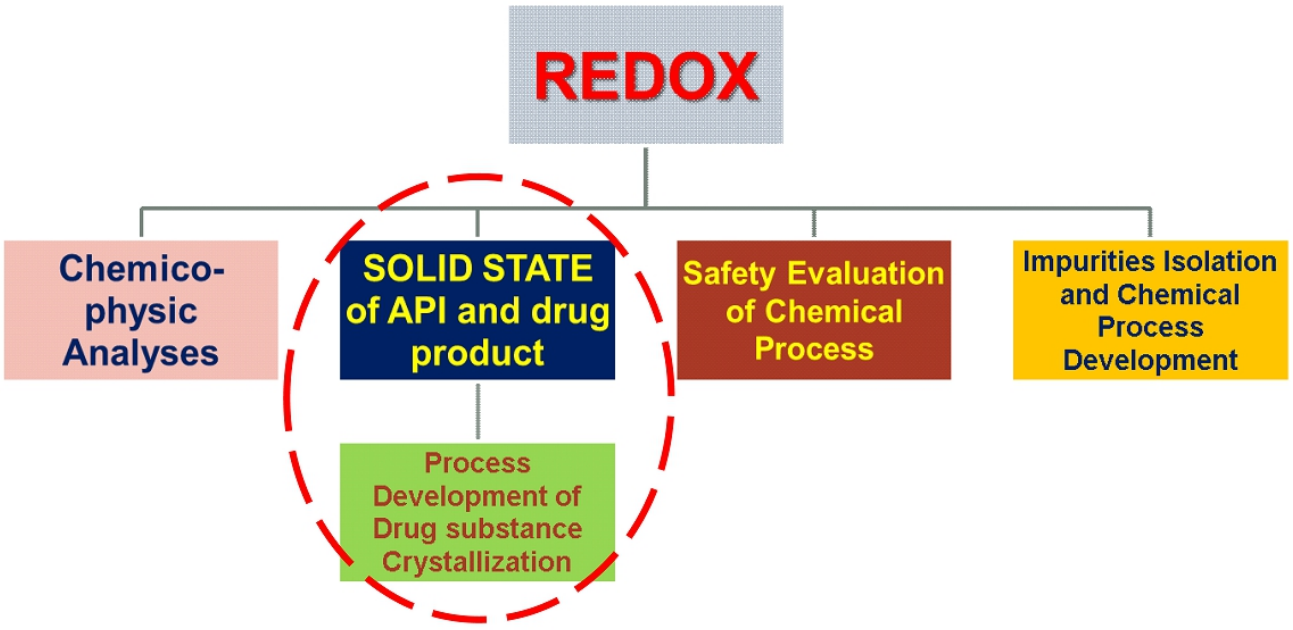
New Drug Product

Clinical-stage biopharmaceutical

TONIX PHARMACEUTICALS







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**B. Daugherty**
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# Thanks for your attention

**Exhibit 99.03**

TONIX PHARMACEUTICALS

# Pharmacokinetic Properties of TNX-102 SL, a Sublingual Formulation of Cyclobenzaprine Hydrochloride

**Bruce Daugherty, PhD**

**11th Pharmaceutics and Novel Drug Delivery Systems (PDDS) Conference 2024 – Oral Presentation**
**September 19, 2024**
**Rome, Italy**



Version 1513 September 12, 2024 (P0601)

## Cautionary Note on Forward-Looking Statements

Certain statements in this presentation regarding strategic plans, expectations and objectives for future operations or results are “forward-looking statements” as defined by the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as “anticipate,” “believe,” “forecast,” “estimate” and “intend,” among others. These forward-looking statements are based on Tonix’s current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, the risks related to failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; risks related to the failure to successfully market any of our products; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2023, as filed with the Securities and Exchange Commission (the “SEC”) on April 1, 2024, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.

TONIX PHARMACEUTICALS

## Disclosure

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Lesley Arnold

**RHO**
Ben Vaughn

**SYNEOS HEALTH**

**PREMIER RESEARCH**

#**Poster**: Friday, Sept 20 "The importance of in vitro discriminatory tests in the development of a sublingual dosage form of TNX-102 SL (Cyclobenzaprine HCl) tablets

*Own stock and/or stock options in Tonix



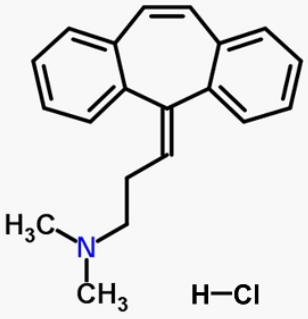


## Outline

- Clinical Pharmacology of TNX-102 SL
  - Single dose
  - Multiple dose
  - Dose proportionality and food effect
- Phase 3 Efficacy and Safety of TNX-102 SL in Fibromyalgia

CNS PORTFOLIO

## Cyclobenzaprine-HCl and TNX-102 SL*




**Cyclobenzaprine Hydrochloride**

*Flexeril® 10 mg T.I.D. approved for the treatment of muscle spasm (Merck 1977)*

**TNX-102 SL Tablet 2.8 mg**

**TNX-102 SL is an investigational new drug and not approved for any indication*

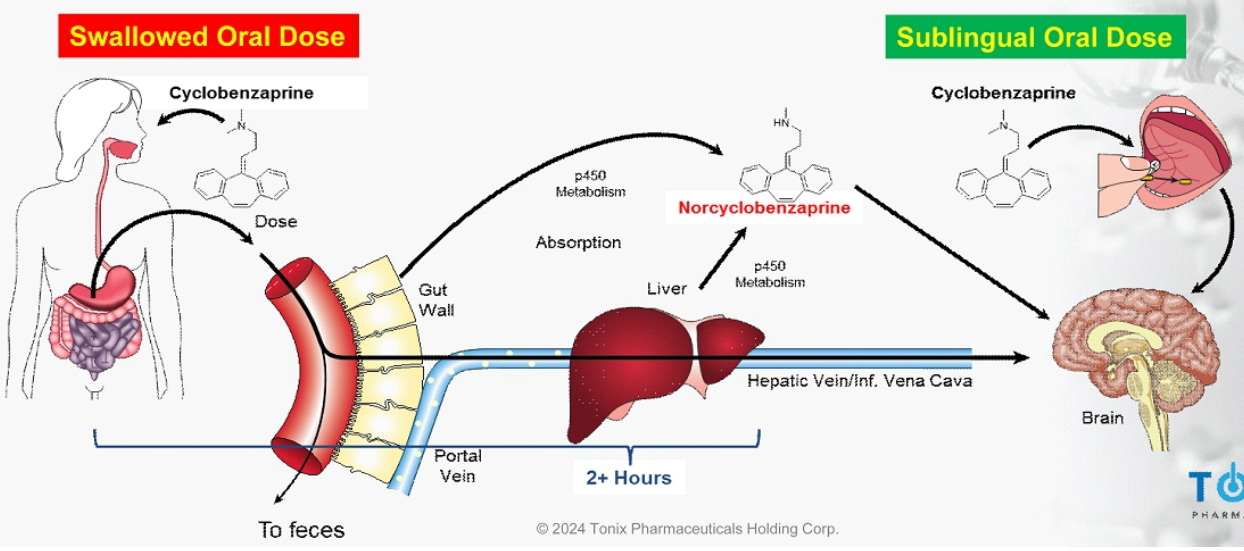






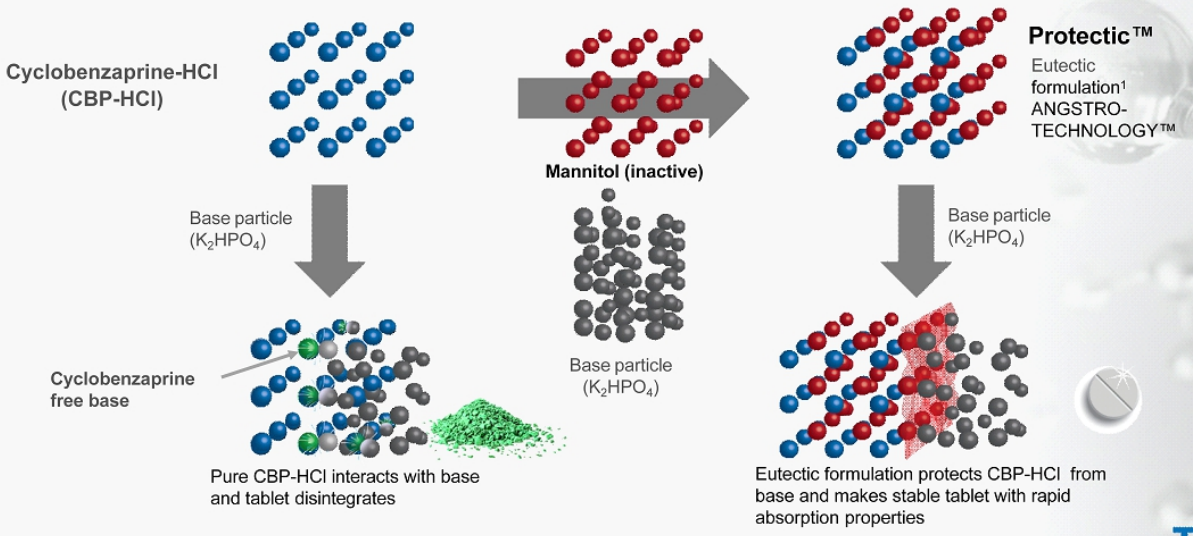
## TNX-102 SL: Sublingual Administration and Transmucosal Delivery

- Faster absorption provides pharmacokinetics that is designed for bedtime dosing
- Bypasses "first-pass" metabolism
- Reduced metabolism of parent cyclobenzaprine to active metabolite norcyclobenzaprine



# TNX-102 SL: Proprietary Eutectic Formulation

## Proprietary Cyclobenzaprine HCl Eutectic Mixture Stabilizes Sublingual Tablet Formulation




[1] U.S. Patent issued May 2, 2017

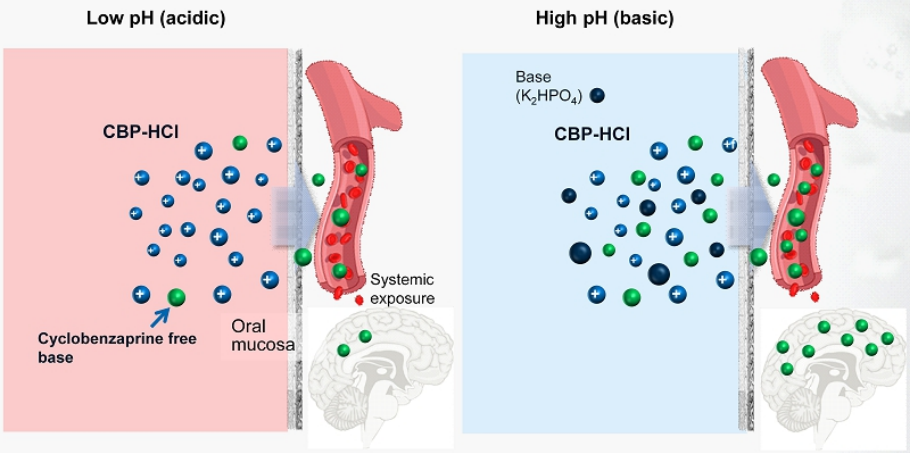






# Formulation with Base Increases Systemic Absorption of Sublingual Cyclobenzaprine[1]

## Concentration gradient increases diffusion of free base across oral mucosa (Le Chatelier's Principle)




[1]US Patent applications 13/918,692. 14/214,433 and 14/776,624 - Eutectic Formulations

## TNX-102 SL Pharmacokinetic Study – Single Dose 2.8 mg

### Objectives

- Single center, comparative, randomized, single-dose, open-label, parallel-design
- Compare the rate and extent of absorption of 3 test formulations of TNX-102 SL 2.8 mg tablets vs commercial cyclobenzaprine HCl 5 mg IR tablet
- Assess safety and tolerability of TNX-102 SL tablets (2.8 mg) vs commercial cyclobenzaprine HCl IR 5 mg tablet
- Select optimal formulation for further clinical development

### Demographics

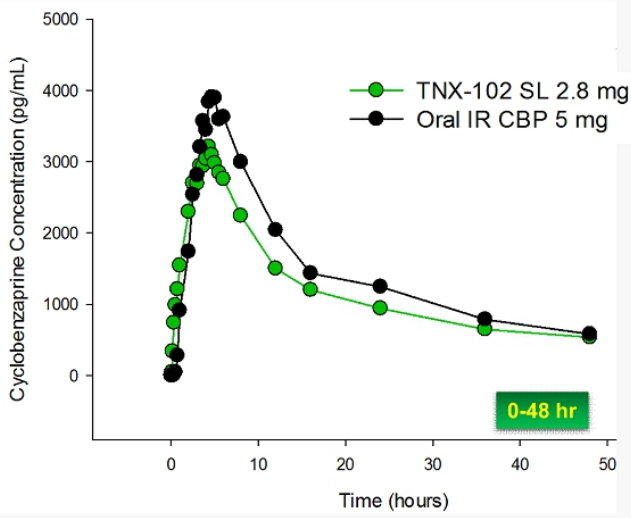
- 58% Female
- 96% White
- 13% Hispanic
- Aged 19-59 years (mean = 36.2 years)
- N = 24







## TNX-102 SL Pharmacokinetics: Comparison with Oral IR



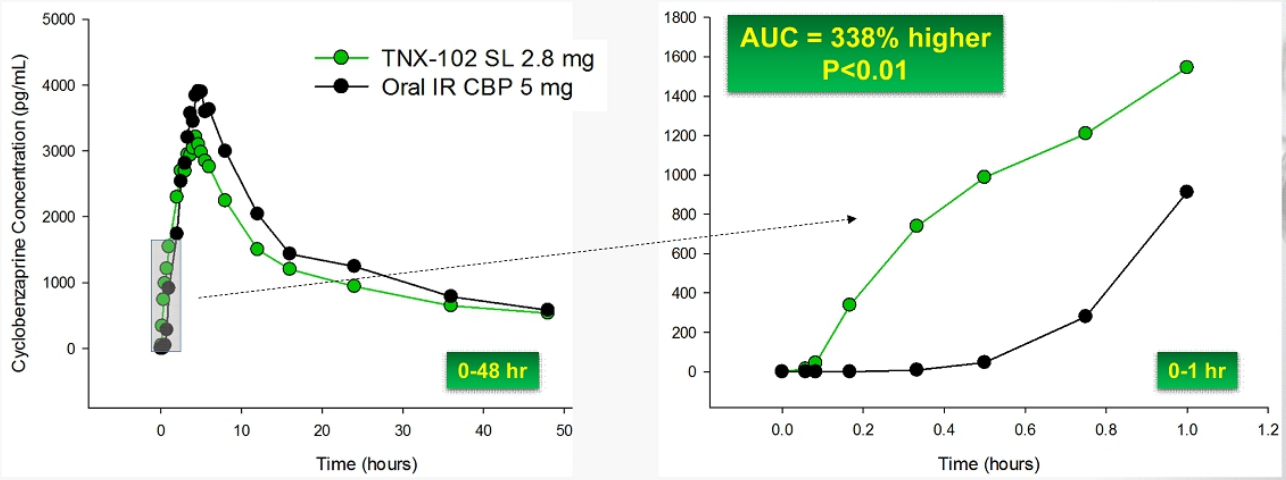

| Parameter | TNX-102 SL 2.8 mg | Oral IR CBP 5 mg |
|---|---|---|
| $C_{max}$ (ng/mL) | 3.4 | 4.3 |
| $AUC_{0-48}$ (ng•hr/mL) | 57.4 | 69.5 |
| $T_{1/2}$ (hr) | 27.4 | 25.1 |

Tablet dose = 44% lower

$C_{max}$ = 20% lower

$AUC_{0-48}$ = 17% lower

# TNX-102 SL Exhibits Rapid Systemic Exposure of Cyclobenzaprine Post SL Administration




Absorption Time Lag ($T_{lag}$) = 12 times faster

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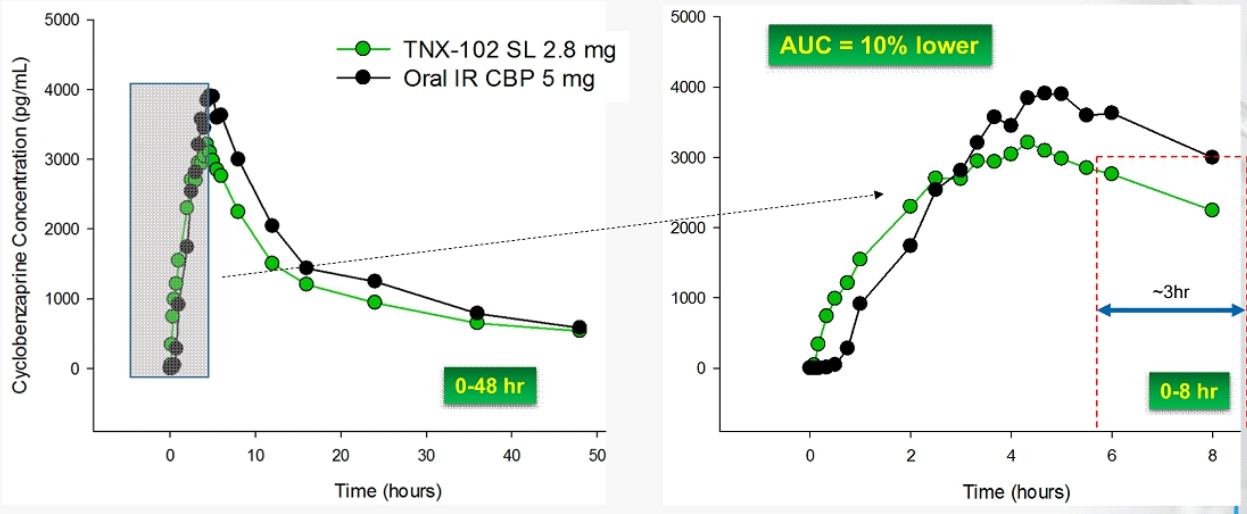
# TNX-102 SL Exhibits a Targeted Systemic Exposure Pattern of Cyclobenzaprine During Sleep

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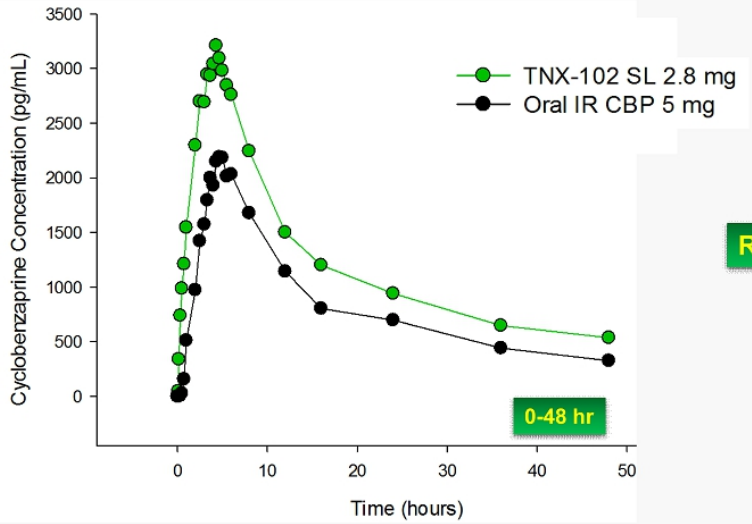
## TNX-102 SL Exhibits Higher Bioavailability Upon Dose Normalization of Oral IR 5 mg to 2.8 mg




**Relative Bioavailability = 154% of Oral IR**

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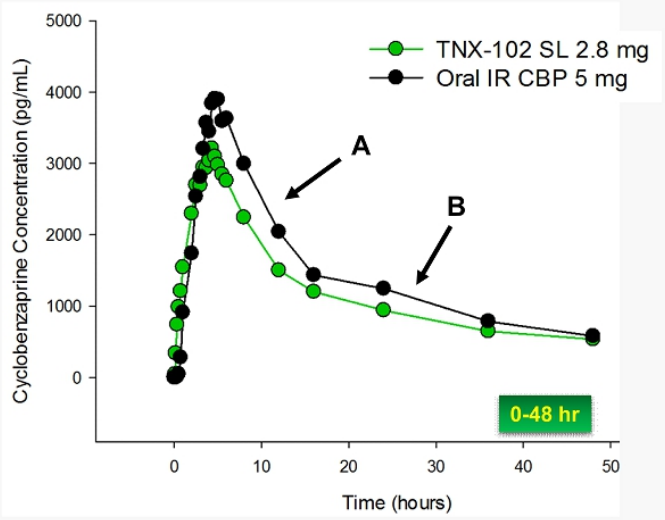
## Multi-Compartment Pharmacokinetic Model for Cyclobenzaprine




**A) Distribution Phase**

- Distribution from circulation into body tissues
- TNX-102 SL rapid elimination half-life = 3.1 hr

**B) Elimination Phase**

- Drug metabolism and secretion
- TNX-102 SL terminal elimination half-life = 27 hr

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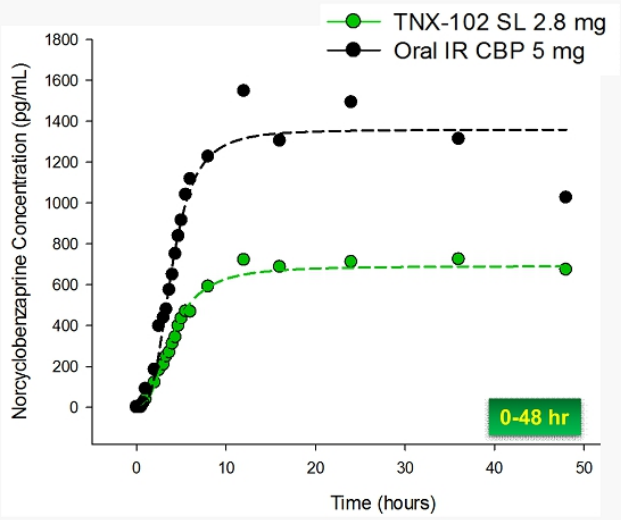
## TNX-102 SL Pharmacokinetics: Norcyclobenzaprine is the Long-Lived Major Metabolite




| Parameter | TNX-102 SL 2.8 mg | Oral IR CBP 5 mg |
|---|---|---|
| $C_{max}$ (ng/mL) | 0.81 | 1.71 |
| $AUC_{0-48}$ (ng•hr/mL) | 30.5 | 58.6 |
| $T_{1/2}$ (hr) | 72.0 | 66.7 |

$C_{max}$ = 53% lower

$AUC_{0-48}$ = 48% lower

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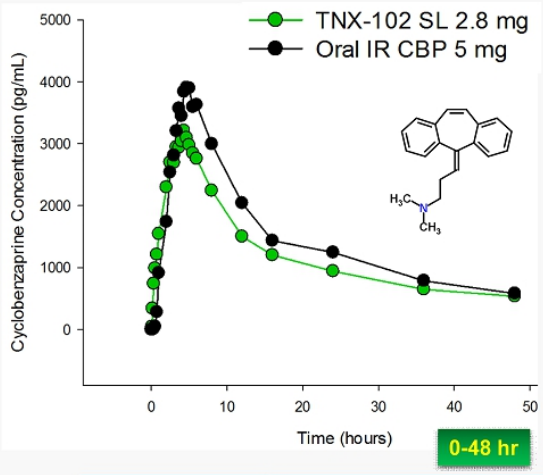
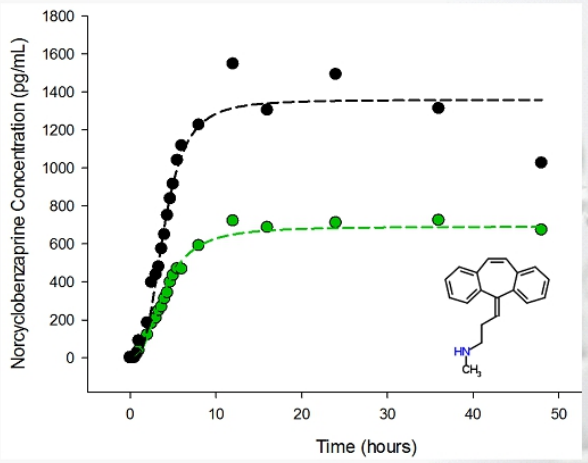
## Ratio of Cyclobenzaprine/Norcyclobenzaprine Exposure is Increased with TNX-102 SL




| | TNX-102 SL 2.8 mg | Oral IR 5 mg |
|---|---|---|
| $AUC_{0-48}$ CBP/nCBP | 1.88 | 1.18 |

$AUC_{0-48}$ (CBP/nCBP) = 59% higher

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## TNX-102 SL: Single Dose PK Differentiation from Oral IR CBP

**TNX-102 SL 2.8 mg v. Oral IR CBP 5 mg: Single Dose Pharmacokinetics**

| Parameter | TNX-102 SL 2.8 mg | Oral IR CBP 5 mg | TNX-102 SL Compared to Oral IR |
|---|---|---|---|
| | Cyclobenzaprine | | |
| **Absorption Lag Time** | 0.050 hr (3 min) | 0.622 hr (37 min) | 12x faster |
| **Relative Bioavailability** | 154% | - | 54% higher |
| **$C_{max}$** | 3.41 ng/mL | 4.26 ng/mL | 20% lower |
| **$AUC_{0-48}$** | 57.4 ng•hr/mL | 69.5 ng•hr/mL | 17% lower |
| | Norcyclobenzaprine | | |
| **$C_{max}$** | 0.81 ng/mL | 1.71 ng/mL | 53% lower |
| **$AUC_{0-48}$** | 30.5 ng•hr/mL | 58.6 ng•hr/mL | 48% lower |
| | Cyclobenzaprine/Norcyclobenzaprine | | |
| **Ratio $AUC_{0-48}$** | 1.88 | 1.18 | 59% higher |

PK = pharmacokinetics
IR = immediate release
CBP = cyclobenzaprine
$C_{max}$ = maximum concentration
AUC = Area under the curve







## Multi-Functional Mechanism Involves Antagonism at Four Neuronal Receptors

### Active ingredient, cyclobenzaprine, interacts with four receptors

- **Antagonist at 5-$HT_{2A}$ receptors**
  - Similar activity to Desyrel® (trazodone) and Nuplazid® (pimivanserin)
- **Antagonist at $\alpha_1$-adrenergic receptor**
  - Similar activity to Minipress® (prazosin)
- **Antagonist at histamine $H_1$ receptors**
  - Similar activity to Benadryl® (diphenhydramine) and Vistaril® (hydroxyzine)
- **Antagonist at muscarinic $M_1$ receptors**
  - Similar activity to Benadryl® (diphenhydramine), Prozac® (fluoxetine), Paxil® (paroxetine), Zyprexa (olanzapine) and Seroquel® (quetiapine)

## Cyclobenzaprine Binding Affinities for Receptors and Transporters

**Receptors believed to have a role in sleep quality**

| | $H_1$ | 5-$HT_{2A}$ | $\alpha_{1A}$ | $M_1$ | $\alpha_{1B}$ | $D_1$ | SERT | NET |
|---|---|---|---|---|---|---|---|---|
| Cyclobenzaprine | 1.3 | 5.2 | 5.6 | 7.9 | 9.1 | 12 | 29 | 35 |
| Norcyclobenzaprine | 5.6 | 13 | 34 | 30 | 11 | 57 | 91 | 2.6 |

**CBP/nCBP Activity** — Antagonist | Inhibitor

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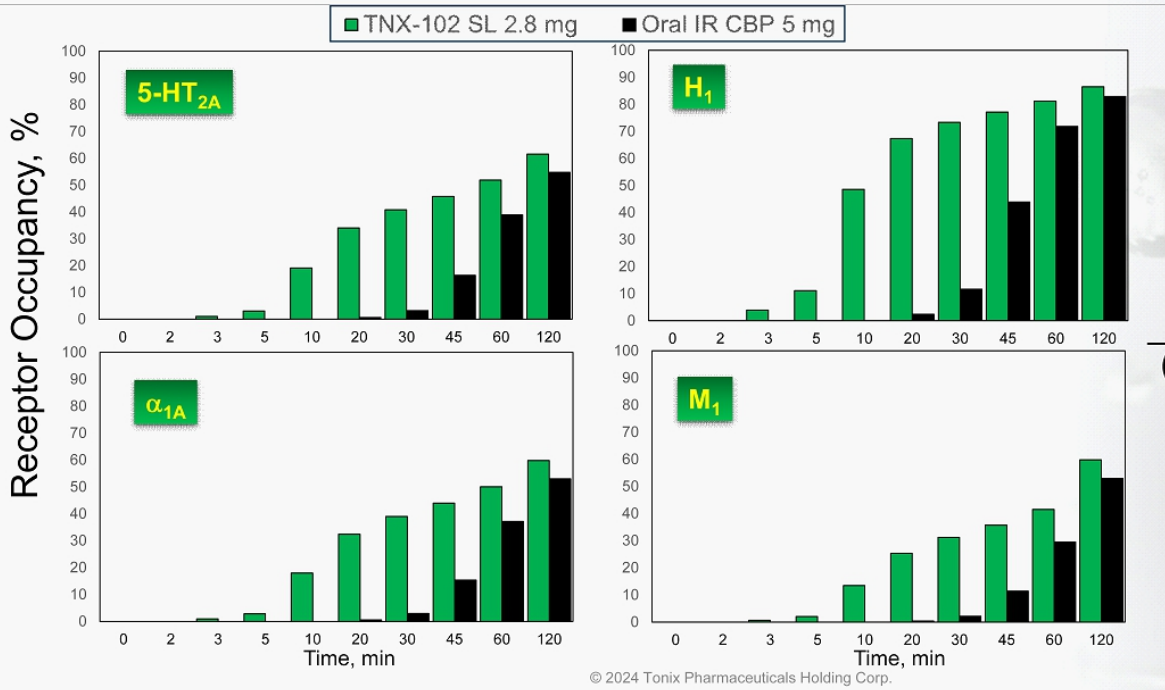
## Receptor Occupancy from 0-2 hr Post Administration TNX-102 SL 2.8 mg vs Oral IR 5 mg




$$\frac{[D]}{([D] + K_i)}$$

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## TNX-102 SL Pharmacokinetic Study – Multiple Dose 5.6 mg

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### Objectives

- Single center, comparative, randomized, multiple-dose, open-label, parallel-design
- Compare the rate and extent of absorption of TNX-102 SL tablets (2 x 2.8 mg) vs AMRIX® 30 mg extended-release capsule once daily for 20 days
- Assess safety and tolerability of TNX-102 SL tablets (2 x 2.8 mg) vs AMRIX® 30 mg extended release
- Compare systemic absorption and metabolic profile of the 2 products at steady state

### Demographics

- 47% Female
- 95% White
- 15% Hispanic
- Aged 23-75 years (mean = 43.4 years)
- N = 60

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## Pharmacokinetic Study by Treatment Day – Day 1 vs Day 20

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Plasma Cyclobenzaprine, pg/mL

Time, hours

| Parameter | TNX-102 SL 5.6 mg (N=26) | AMRIX® 30 mg (N=30) |
|---|---|---|
| $AUC_{0-\tau, ss}$ (ng*h/mL) | 174.7 ± 101.5 | 669.7 ± 204.5 |
| $C_{max, ss}$ (ng/mL) | 11.2 ± 5.7 | 39.6 ± 11.9 |
| $T_{max}$ (h) | 5.0 (2.0-9.0) | 7.0 (5.0-9.0) |
| $T_{1/2}$ (h) | 40.3 ± 10.4 | 35.6 ± 8.2 |
| $C_{max}$ (accum) | 2.1-fold | 3.1-fold |
| AUC (accum) | 2.5-fold | 3.7-fold |

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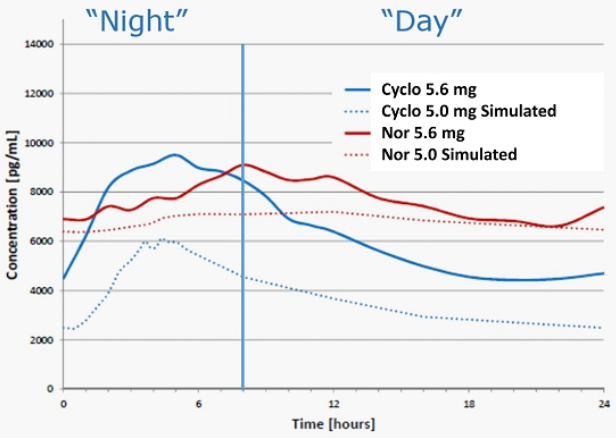
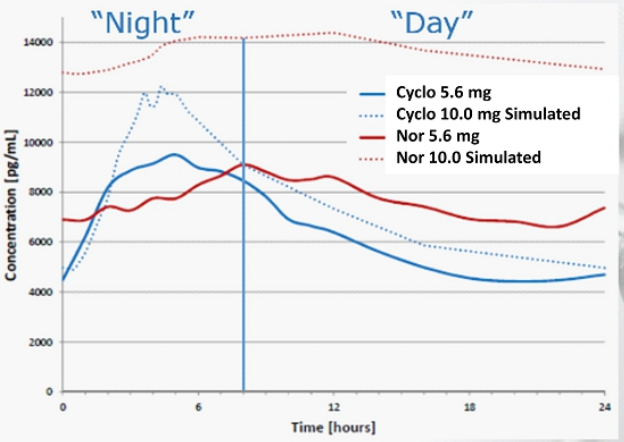
# Concentration-Time Profiles for TNX-102 SL 5.6 mg vs. Simulated Oral IR Cyclobenzaprine 5 and 10 mg – Day 20




- **Rapid systemic exposure**
- **Increases bioavailability during sleep**
- **Avoids first-pass metabolism**
- **Lowers exposure to long-lived active major metabolite, norcyclobenzaprine**
- **Cyclobenzaprine undergoes extensive first-pass metabolism when orally ingested**





# TNX-102 SL Pharmacokinetic Study - Dose Proportionality and Food Effect



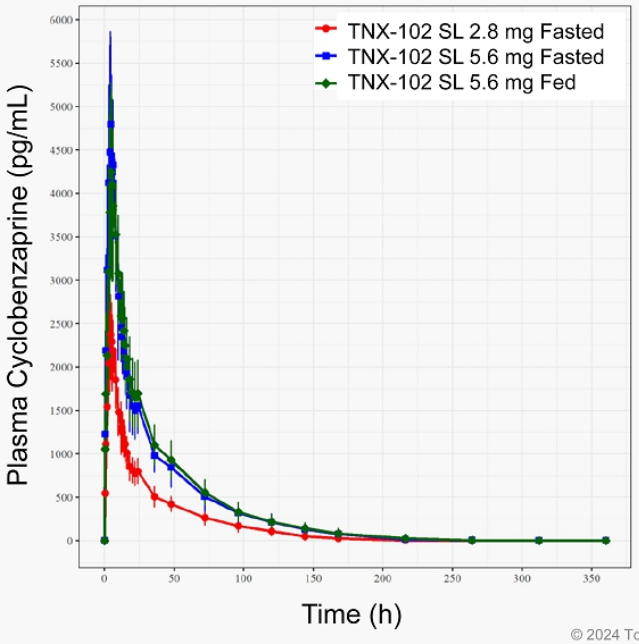
## Objectives

- Single center, comparative, randomized, single-dose, 3-period, 6-sequence crossover
- Evaluate the dose proportionality of TNX-102 SL 2.8 mg vs 5.6 mg under fasted conditions
- Evaluate the effect of food on TNX-102 SL 5.6 mg
- Assess safety and tolerability of TNX-102 SL tablets in healthy subjects

## Demographics

- 50% Female
- 100% White
- 12.5% Hispanic
- Aged 36-62 years (mean = 52.7 years)
- N = 15

# TNX-102 SL PHARMACOKINETIC STUDY - DOSE PROPORTIONALITY AND FOOD EFFECT




| Parameter | 2.8 mg Fasted (N=15) | 5.6 mg Fasted (N=16) | 5.6 mg Fed (N=16) |
|---|---|---|---|
| $AUC_{0-t}$ (ng*h/mL) | 64.4 ± 14.1 | 128.1 ± 27.6 | 133.1 ± 27.6 |
| $C_{max}$ (ng/mL) | 2.5 ± 0.4 | 5.1 ± 1.0 | 4.5 ± 1.0 |
| $T_{max}$ (h) | 4.3 (1.0-5.7) | 4.3 (1.0-5.7) | 4.7 (4.0-10.0) |
| $T_{1/2}$ (h) | 35.4 ± 7.2 | 36.4 ± 7.6 | 37.9 ± 7.1 |





# Fibromyalgia is a Large, Underserved and Dissatisfied Population



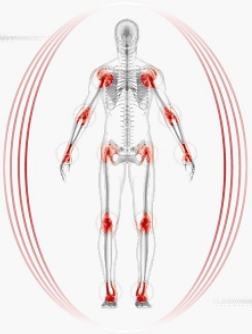
- **More than 10 million U.S. adults are affected – predominantly women**[1,2]
  - Debilitating and life altering condition
  - Significant economic impact
- **Patients are dissatisfied, despite three FDA approved drugs**[3,4]
  - 85% of patients fail first-line therapy[5]: efficacy variability, tolerability issues especially when used long-term and lack of broad-spectrum activity
  - Typical for patients to rotate between drugs and be on multiple drugs at the same time; 79% of FM patients are on multiple therapies[5]
- **~2.7 million FM patients diagnosed and treated**[6]
  - >22 million prescriptions are issued for the treatment of fibromyalgia (on- and off-label usage) each year[7,8]
- **No new R*x* product since 2009**
- *The treatment objective is to **restore functionality** and **quality of life** by broadly improving symptoms while avoiding significant side effects*

[1]American College of Rheumatology (www.ACRPatientInfo.org accessed May 7, 2019) – prevalence rate of 2-4% for U.S. adult population (~250 million)
[2]Vincent A, et al. *Arthritis Care Res (Hoboken)*. 2013 65(5):786-92. doi: 10.1002; diagnosed prevalence rate was 1.1% of adult population or 50% of the prevalent population
[3]Robinson RL, et al. *Pain Med.* 2012 13(10):1366-76. doi: 10.1111; 85% received drug treatment
[4]The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica); Duloxetine (Cymbalta); Milnacipran (Savella)
[5]EVERSANA primary physician research, May 2024; commissioned by Tonix
[6]EVERSANA analysis of claims database, May 2024; commissioned by Tonix
[7]Product sales derived from IMS MIDAS; IMS NDTI used to factor usage for fibromyalgia; data accessed April 2015.
[8]Market research by Frost & Sullivan, commissioned by Tonix, 2011

## Chronic Overlapping Pain Conditions (COPC) Believed to Result from Shared Brain Processes

- COPC is a set of disorders that coaggregate; these disorders can include but are not limited to[1,2]:

- Temporomandibular disorder
- **Fibromyalgia**
- Irritable bowel syndrome
- Vulvodynia
- CFS/ME[3]
- Interstitial cystitis/painful bladder syndrome



- Endometriosis
- Chronic tension-type headache
- Migraine headache
- Chronic lower back pain

- Similar central mechanisms play significant roles in all pain conditions, even those with known peripheral contributions[1,2]

[1]Maixner W, et al. *J Pain*. 2016;17(9 Suppl):T93-T107.
[2]Veasley C, et al. http://www.chronicpainresearch. org/public/CPRA_WhitePaper_2015-FINAL-Digital.pdf. Published May 2015. Accessed July 26, 2021.
[3]CFS/ME – chronic fatigue syndrome/myalgic encephalomyelitis



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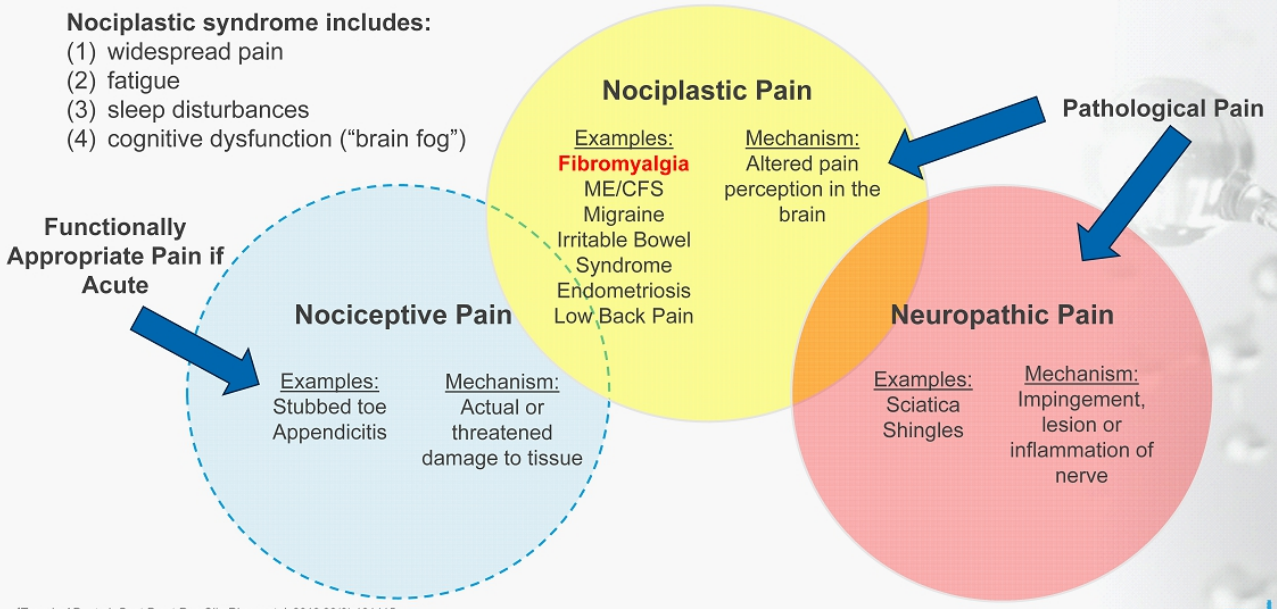
## The Third Primary Type of Pain: Nociplastic Pain[1-4]

**Nociplastic syndrome includes:**
(1) widespread pain
(2) fatigue
(3) sleep disturbances
(4) cognitive dysfunction (“brain fog”)




[1]Trouvin AP, et al. *Best Pract Res Clin Rheumatol*. 2019;33(3):101415.
[2]Fitzcharles MA, et al. *Lancet* 2021;397:2098-110
[3]Kaplan CM, et al. *Nat Rev Neurol*. 2024 20(6):347-363..
[4]Clauw DJ. *Ann Rheum Dis*. 2024 ard-2023-225327. doi: 10.1136/ard-2023-225327.



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## About Fibromyalgia

*Fibromyalgia is a **chronic pain disorder** resulting from **amplified sensory** and **pain signaling** within the CNS*[1]

*Fibromyalgia is a **syndrome** comprised of the **symptoms**: chronic widespread pain, **nonrestorative sleep**, and fatigue*


**Fibromyalgia is** considered a **chronic overlapping pain condition (COPC)**
*- the **only COPC** with any **FDA-approved drugs***[3]

**Fibromyalgia is the prototypic nociplastic syndrome**

[1]American Chronic Pain Association (www.theacpa.org, 2019)
[3]CFS/ME = chronic fatigue syndrome/myalgic encephalomyelitis
[3]The three drugs with FDA approval for the treatment of fibromyalgia: Pregabalin (Lyrica®); Duloxetine (Cymbalta®); Milnacipran (Savella®)





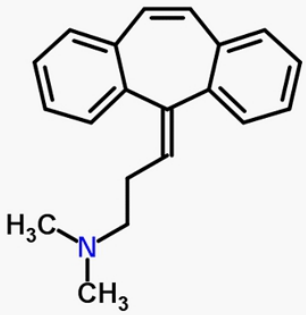


## Fibromyalgia: Unrefreshing Sleep and Cyclobenzaprine Treatment

- **Non-restorative sleep**[1,2]
  - Harvey Moldofsky – recognition of unrefreshing/non-restorative sleep:
    - Symptom
    - Potential causative or potentiating factor
- **Cyclobenzaprine**[3,9]
  - Potentially the earliest drug studied in fibromyalgia as an oral swallowed agent
  - Studies showed equivocal effects and tolerability issues at “muscle spasm” doses
- **Bedtime, *low-dose* cyclobenzaprine targeting non-restorative sleep**[10-11]
  - Recognition of unrefreshing sleep as a target of therapy
  - Primitive oral, swallowed formulation – “flat” pharmacokinetics
- **Bedtime, *sublingual transmucosal* cyclobenzaprine targeting non-restorative sleep**[12]
  - Dynamic pharmacokinetic profile, rapid absorption, decrease in major metabolite
  - Two studies (Phase 2 and Phase 3) at 2.8 mg; three Phase 3 studies at 5.6 mg.

[1]Moldofsky H et al. *Psychosom Med.* 1975. 37:341-51.
[2]Moldofsky H and Scarisbrick P. *Psychosom Med.* 1976. 38:35-44.
[3]Bennett RM, et al. *Arthritis Rheum* 1988. 31:1535–42.
[4]Quimby LG, et al. *J Rheumatol Suppl,* 1989 Nov;19:140–3.
[5]Reynolds WJ, et al. *J Rheumatol.* 1991.18:452–4.
[6]Santandrea S, et al. *J Int Med Res.* 1993.21:74–80.
[7]Cantini F, et al. *Minerva Med.* 1994. 85:97–100.
[8]Carette S, et al. *Arthritis Rheum.* 1994. 37:32–40.
[9]Tofferi JK, et al. *Arthritis Rheum.* 2004. 51:9–13.*1*
[10]Iglehart IW. 2003; US Patent 6,541,523.
[11]Moldofsky et al. *J Rheumatol.* 2011. 38:2653-2663
[12]Lederman S et al. *Arthritis Care Res.* 2023. 75:2359-2368.

## Cyclobenzaprine Long-Term Utilization




- **Flexeril® approved in 1977 by Merck for the treatment of muscle spasm**
  - 10 mg T.I.D. for acute use (2-3 weeks)
  - Original NDA included "*8 long term safety studies* in which patients with various neurologic disorders received cyclobenzaprine up to *80 mg per day for 1 month up to 3 years*."[1]
- **6 published studies in fibromyalgia**[2-8]
  - N=246, placebo controlled, 4-24 week treatment period
  - Generally well tolerated, no new or unexpected AEs
- **Extensive safety record in humans for over 30 years**
  - Widely used in the U.S., ~20 million prescriptions and ~ 1 billion tablets dispensed *per year*[9]
  - Chronic cyclobenzaprine use is common *(*~12% of users)[9]
- **Post-marketing surveillance program**[1]
  - 7,607 patients included 297 patients treated with 10 mgs for ≥ 30 days
  - Incidence of most common AEs was much lower than in controlled studies

[1]1999 Merck OTC AdCom Briefing Package
[2]Bennett RM, et al. *Arthritis Rheum* 1988. 31:1535–42.
[3]Quimby LG, et al. *J Rheumatol Suppl*, 1989 Nov;19:140–3.
[4]Reynolds WJ, et al. *J Rheumatol*. 1991.18:452–4.
[5]Santandrea S, et al. *J Int Med Res*. 1993.21:74–80.
[6]Cantini F, et al. *Minerva Med*. 1994. 85:97–100.
[7]Carette S, et al. *Arthritis Rheum*. 1994. 37:32–40.
[8]Tofferi JK, et al. *Arthritis Rheum*. 2004. 51:9–13.*1*
[9]IMS report 2011 of cyclobenzaprine use in 2009 – Data on File







## TNX-102 SL: Phase 3 *RESILIENT* Study Design

RESILIENT Study

### General study characteristics:

- Randomized, double-blind, multicenter, placebo-controlled study in fibromyalgia
- 33 U.S. sites enrolled 457 participants with fibromyalgia as defined by 2016 Revisions to the 2010/2011 FM Diagnostic Criteria[1]
- Aged: 18-65 years (mean = 49.4 years); FM diagnosis: mean = 9.2 years; 94.5% female; 84.6% white
- Average self-reported pain at baseline = 5.9 out of 10
- 366 (80.1%) completed the trial

### Primary Endpoint:

- Change from baseline to Week 14 (TNX-102 SL vs. placebo) in weekly averages of daily diary average pain severity score

**TNX-102 SL once-daily at bedtime**

**Placebo once-daily at bedtime**

***14 weeks***

**Two-week run-in at 2.8 mg dose at bedtime followed by 12 weeks at 5.6 mg (2 x 2.8 mg) dose**

**Study Title**: A Phase 3 Study to Evaluate the Efficacy and Safety of TNX-102 SL Taken Daily in Patients With Fibromyalgia (RESILIENT)

**Trial ID**: TNY-CY-F307 ('RESILIENT')

**ClinicalTrials.gov Identifier**: NCT05273749

[1]Wolfe F, et al. *Semin Arthritis Rheum*. 2016 46(3):319-329. doi: 10.1016

# *RESILIENT* Primary Outcome Measure
## *Reduction in Widespread Pain*

RESILIENT Study

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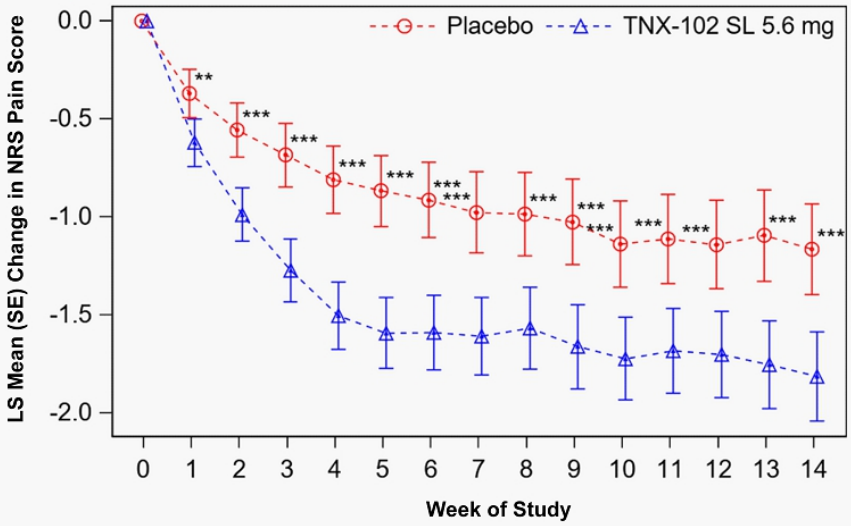
### Weekly Average of Daily Diary NRS Ratings of Average Pain Over Prior 24 Hours




**Effect Size = 0.38**
***p* = 0.00005#**

N = 225

N = 231

**p<0.001; ***p<0.0001

**Week 14 LS mean (SE) change from baseline for TNX-102 SL -1.82 (0.12) and for placebo -1.16 (0.12); LSMD from placebo -0.65 (0.16)**

#Based on Mixed Model Repeated Measures with Multiple Imputation, with fixed categorical effects of treatment, center, study week, and treatment by study week interaction, as well as baseline value and baseline value-by-study week interaction. Abbreviations: LS, least squares; LSMD, least squares mean difference; NRS, numerical rating scale; SE, standard error

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# *RESILIENT* Continuous Pain Responder Graph

RESILIENT Study

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**30% Responders#**
**(45.9% vs 27.1%)**
**p < 0.001**

**50% Responders#**
**(22.5% vs 13.3%)**
**p = 0.011**

#Analyses: Pearson's Chi Squared test for equality of proportions
Abbreviations: CI, confidence interval; DIP, difference in proportions
^pre-specified analyses but not key secondary analyses

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## RESILIENT Safety

RESILIENT Study

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### Treatment-Emergent Adverse Events (TEAEs) at Rate of ≥ 3% in Either Treatment Group

| System Organ Class<br>Preferred Term | TNX-102 SL<br>N=231 | Placebo<br>N=226 | Total*<br>N=457 |
|---|---|---|---|
| **Systemic Adverse Events** | | | |
| COVID-19 | 10 (4.3%) | 7 (3.1%) | 17 (3.7%) |
| Somnolence | 7 (3.0%) | 3 (1.3%) | 10 (2.2%) |
| Headache | 7 (3.0%) | 4 (1.8%) | 11 (2.4%) |
| **Oral Cavity Adverse Events** | | | |
| Hypoaesthesia oral | 55 (23.8%) | 1 (0.4%) | 56 (12.3%) |
| Product taste abnormal | 27 (11.7%) | 2 (0.9%) | 29 (6.3%) |
| Paraesthesia oral | 16 (6.9%) | 2 (0.9%) | 18 (3.9%) |
| Tongue discomfort | 16 (6.9%) | 0 (0.0%) | 16 (3.5%) |

***No clinically meaningful differences in mean systolic blood pressure, diastolic blood pressure and weight between treatment groups***

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## TNX-102 SL Showed Broad-Spectrum Activity and was Well Tolerated

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| | | Lyrica® | Cymbalta® Savella® | TNX-102 SL |
|---|---|---|---|---|
| Activity | Pain | + | + | + |
| | Sleep | + | - | + |
| | Fatigue | - | + | + |
| Systemic Tolerability Issues | Insomnia | - | + | - |
| | Fatigue | + | - | - |
| | Weight | + | - | - |
| | Blood Pressure | - | + | - |
| | Sexual function | - | + | - |
| | GI issues | - | + | - |

- TNX-102 SL showed activity in all three measures of pain, sleep, and fatigue
- TNX-102 SL is not associated with any of the commonly reported side effects of the FDA-approved approved drugs

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## Conclusions

***TNX-102 SL: A unique, sublingual formulation of cyclobenzaprine designed to optimize delivery and absorption***

### ❖Clinical Pharmacology of TNX-102 SL

- Rapid systemic exposure during the first 1-2 hr
- Increased bioavailability during sleep
- Reduced exposure to active metabolite
- Dose proportional
- Absence of food effect

### ❖Efficacy and Safety of TNX-102 SL in Fibromyalgia

- Reduction in widespread pain in 14-week study
- Rapid onset of action: *p*-values <0.01 at each weekly time point, including Week 1
- Well-tolerated, side effects limited to the oral cavity
- Non-opioid, centrally-acting analgesic that could provide a new therapeutic option for fibromyalgia patients
- NDA fling in October 2024 with US FDA







# THANK YOU

**Exhibit 99.04**

# 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.

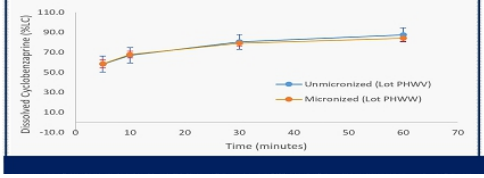
Wetting time is determined by visual examination. It is an in-house developed method which measures the elapsed time for a tablet to become fully wetted or saturated when in contact with water. The wetting time is recorded in seconds.

## 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 |

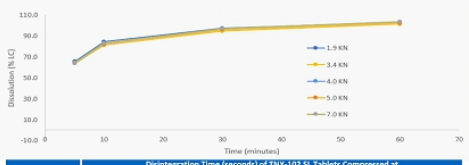
No differences are noted in dissolution profiles for tablets prepared with 80% versus 120% target Crospovidone concentration in the TNX-102 SL (2.8 mg) formulation, while slight differences are noted in wetting and disintegration data, these do not reach statistical significance at the 99% level.

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.

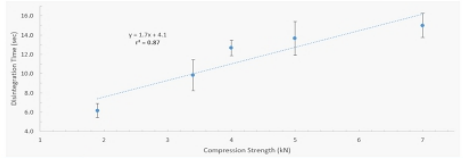
No differences are noted in dissolution, disintegration or wetting time for tablets prepared at 80% versus 120% the target concentration of sodium stearyl fumarate in the TNX-102 SL (2.8 mg) formulation.

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 .

PRESENTED AT PDDS-2024, NH VILLA CARPEGNA VIA PIO IV, 6, 00165 ROMA RM, ITALY SEPTEBER 19, 2024