PCCA Product Info & Testing

LoxaSperse®

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Base, PCCA LoxaSperse® 30-4701

- LoxaSperse is a proprietary blend of specially micronized xylitol with an optimized ratio of micronized poloxamers, designed to improve dispersability and solubility of actives.
- It is an innovative powder excipient base, created for compounding, which is mixed with active ingredients, and then encapsulated or placed in a sachet. The patient opens the capsule or sachet, empties its contents into sterile water or saline, and then immediately irrigates the sinuses with a device.
- According to USP <797>, compounded aqueous solutions for irrigation or nebulization are required to be sterile. (finished preparations that are stored by the patient or pharmacy). LoxaSperse formulations are dry powders.
- Commercially available dry powders for inhalation are manufactured as nonsterile products.

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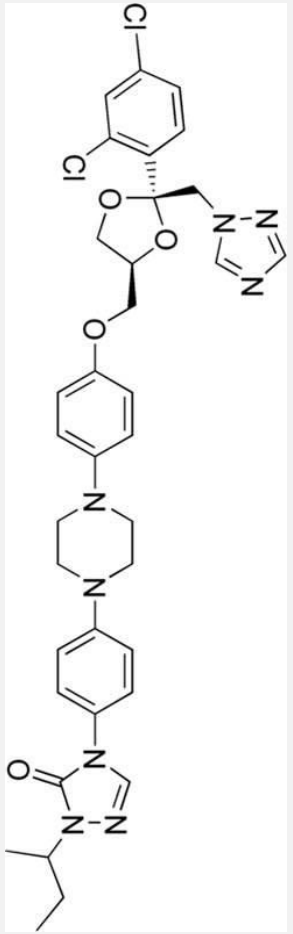
- In addition, it is important to understand and acknowledge that, while a compounded or manufactured aqueous solution for irrigation or nebulization is sterile prior to administration, once the solution is opened and placed into a nebulizer cup or irrigation device, it is no longer sterile.
- LoxaSperse is a base that allows for the preparation of non-sterile capsules and powder sachets, that are added to sterile water or saline by the patient at the moment of administration.
- An additional benefit of using LoxaSperse base is the ability to provide a prolonged beyond-use date since it is a powder (non-aqueous) vehicle.

Overview

1. Particle Size Testing
2. MIC Testing (In Vitro Anti-Fungal Activity)
3. Water Activity

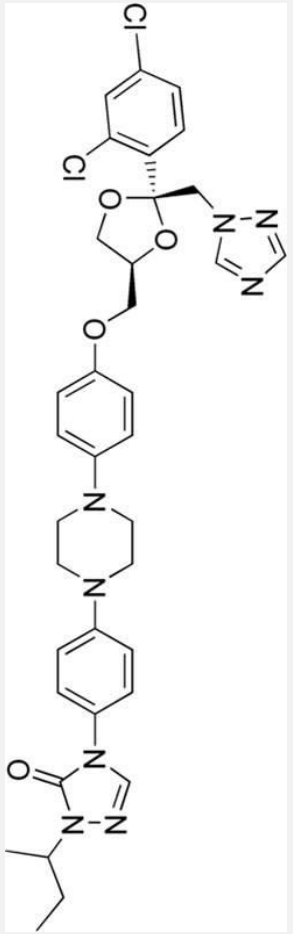
Particle Size Testing (1)

- **Itraconazole**
- Triazole broad spectrum antifungal
- Effective against superficial and systemic mycoses including Aspergillus
- Originally marketed as a capsule formulation
- Highly lipophilic and insoluble in water



Particle Size Testing (1)

- **Itraconazole**
- Powder Particle size: 30 µm
- Reduced particle sizes will enhance drug delivery to the nasal cavity

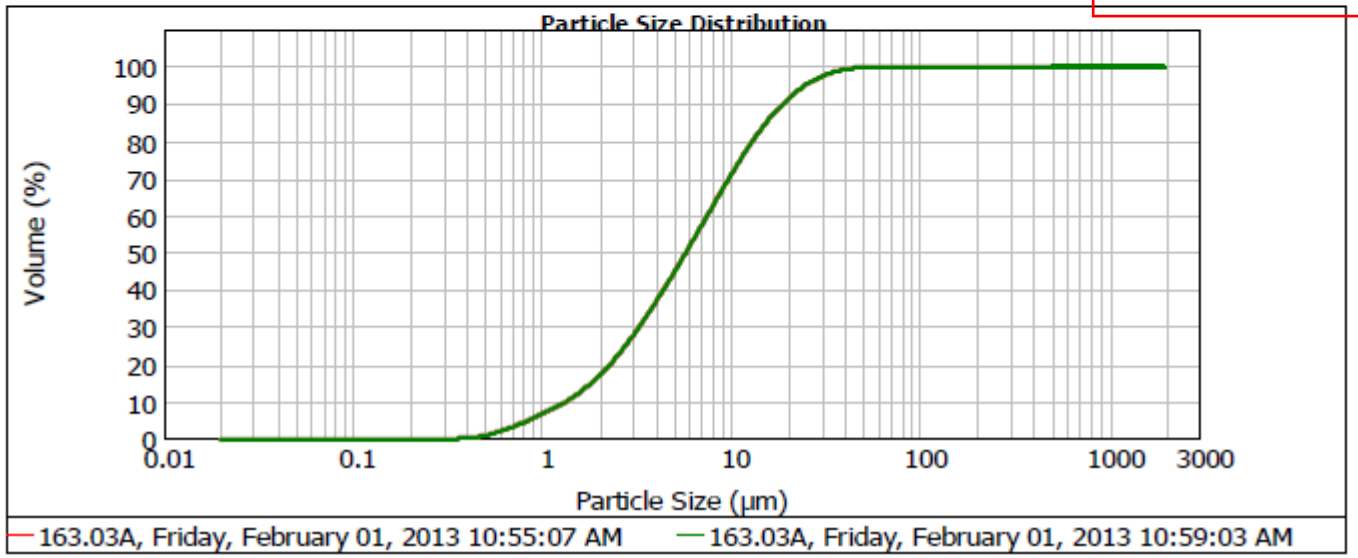


Particle Size Testing (1)

Itraconazole 1%/LoxaSperse 6.4% Suspension in Water – Particle Size Reduction

Particle Name: Pharma. (Generic)	**Accessory Name:** Hydro 2000S (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 1.520	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 5.16 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 2.123 %	**Result Emulation:** Off
Concentration: 0.0025 %Vol	**Span :** 3.009	**Uniformity:** 0.946	**Result units:** Volume
Specific Surface Area: 1.88 m²/g	**Surface Weighted Mean D[3,2]:** 3.186 um	**Vol. Weighted Mean D[4,3]:** 8.300 um	**Mode:** 7.324 um

D10: 1.340 um **D50:** 5.751 um **D90:** 18.645 um

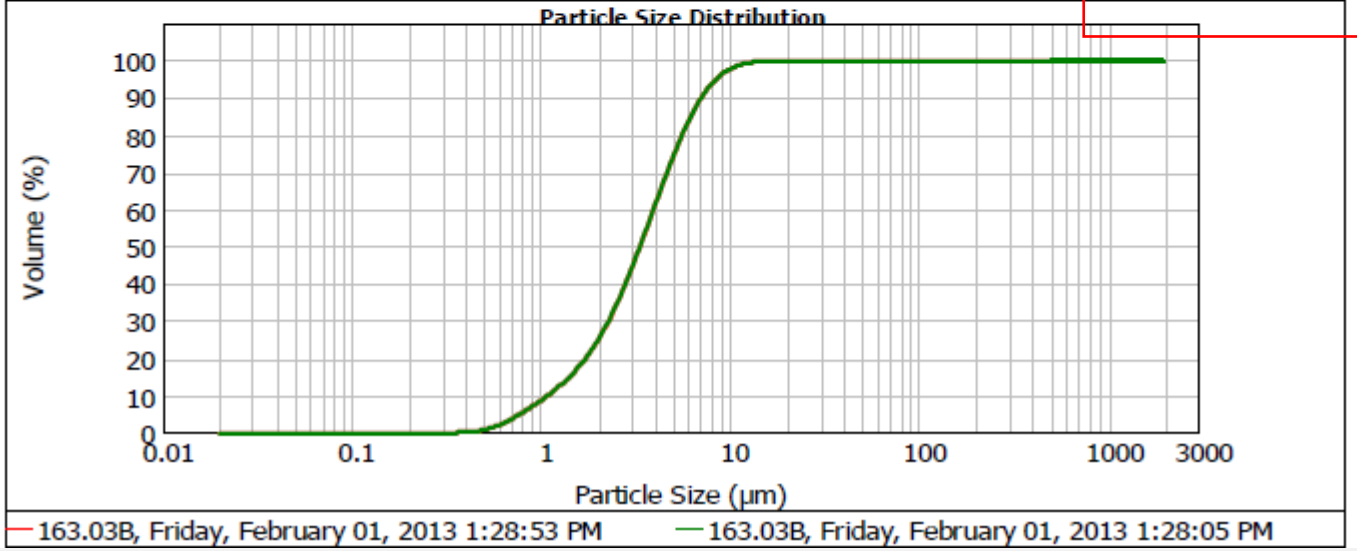


Particle Size Testing (1)

Itraconazole 1%/LoxaSperse 6.4% - Condition After Nebulization – Further Reduction

Particle Name: Pharma. (Generic)	**Accessory Name:** Hydro 2000S (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
Particle RI: 1.520	**Absorption:** 0.1	**Size range:** 0.020 to 2000.000 um	**Obscuration:** 5.14 %
Dispersant Name: Water	**Dispersant RI:** 1.330	**Weighted Residual:** 2.635 %	**Result Emulation:** Off
Concentration: 0.0018 %Vol	**Span :** 1.781	**Uniformity:** 0.555	**Result units:** Volume
Specific Surface Area: 2.59 m²/g	**Surface Weighted Mean D[3,2]:** 2.319 um	**Vol. Weighted Mean D[4,3]:** 3.802 um	**Mode:** 3.869 um

D10: 1.088 um **D50:** 3.330 um **D90:** 7.018 um



Particle Size Testing (1)

Itraconazole 1%/LoxaSperse 6.4%

Conclusion

- LoxaSperse and itraconazole in combination → smaller particle size
- LoxaSperse and itraconazole **after** nebulization decreased by **42%** (D50) compared to before nebulization

In Vitro Anti-Fungal Activity of LoxaSperse Formulations Against a Suite of Fungal Strains (2)

Introduction

3 Articles tested

- LoxaSperse
- LoxaSperse + intraconazole (9:1)
- Intraconazole

Comparator antibiotics

- Amphotericin B
- Fluconazole

CTD (2)

Method: Broth microdilution Minimal Inhibitory Concentration (MIC) assay

Minimum Inhibitory Concentration (MIC) *is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation.*
(A lower MIC is indicative of a better antimicrobial agent)

Table 1. Fungal strains

Strain	Phenotype
A. fumigatus ATCC 204305	Filamentous
A. niger ATCC 16404	Filamentous
C. Albicans ATCC 90028	Yeast
R. oryzae ATCC 9363	Filamentous

MIC Values Against Filamentous Fungi & Yeast Strains (2)

Table 3. MIC values (ug/mL) against filamentous fungi and yeast strains

	A. fumigatus ATCC204305	*A. niger* ATCC16404	*C. albicans* ATCC90028	*R. oryzae* ATCC9363
Itraconazole	0.5	0.5	≤0.125	0.25
Itraconazole + Loxasperse (Intracozole conc.)	0.2	0.2	0.025	0.2

Results:

- MICs are expressed as concentrations of Itraconazole
- MIC values for 2 control antibiotics are consistent with listed breakpoints (NCCLS M38-A; NCCLS M27-A)

Conclusion (2)

- Itraconazole is an effective antifungal drug and MIC values are found to be consistent with MIC breakpoints for all the organisms tested.
- **LoxaSperse + itraconazole have improved antifungal activity against all the fungal strains tested (lower MIC value compared to itraconazole alone).**
- LoxaSperse alone had NO antifungal properties (at tested range of concentrations, which were quite low)
- Amphotericin and fluconazole MIC values are consistent with MIC breakpoints

Water Activity of LoxaSperse Powder

Definition:
Water activity is a measure of how efficiently the water present can take part in a chemical (physical) reaction and/or support microbial growth. If half the water is so tightly bound to a protein molecule that it could not take part in a hydrolysis reaction the overall water activity would be reduced. Water activity (aw) is defined as:

$$aw=p/po$$

Where p and po are the partial pressures of water above the powder and a pure solution under identical conditions respectively. The tightly bound water has no tendency to escape from a powder as a vapor and therefore exerts no partial pressure and has an effective water activity of zero. Water activity is clearly a function of composition but is also a function of temperature.

Water Activity

The approximate water activities of some common foods are given below:

1-0.95	Fresh fruit, meat, milk
0.95-9	Cheese
0.9-0.85	Margarine,
0.85-0.8	Salted meats
0.8-0.75	Jam
0.75-0.65	Nuts
0.65-0.60	Honey
0.5	Pasta
0.3	Cookies
0.2	Dried veg., crackers

Water Activity

Water Activity and Quality (From Food Industry)

Water activity is a critical factor that determines shelf life. Most bacteria, for example, do not grow at water activities below 0.91, including pathogens such as *Clostridium botulinum*. Below 0.80 most molds cannot be grown and below 0.60 no microbiological growth is possible. However, there remain a number of food spoilage microbes that can grow within the range 0.8 - 0.6. The risk of food poisoning must be considered in low acid foods (pH > 4.5) with a water activity greater than aw 0.86. *Staphylococcus aureus*, a common food poisoning organism, can grow down to this relatively low water activity level. Foods that may support the growth of this bacterium include cheese and fermented sausages stored above correct refrigeration temperatures.

Water Activity of LoxaSperse Powder

113365-01	30-4701 Loxasperse w/o Desicant @AmbT Day90 12/16			
Test	*Method Reference*	***Result***	*Units*	*Analysis Start Date*
Water Activity	*Aqua Lab Manual*			
Water Activity		**0.471 @ 25.0**		1/10/2013

113365-02	30-4701Loxasperse w/o Desicant@4C+-1C Day90 12/16			
Test	*Method Reference*	***Result***	*Units*	*Analysis Start Date*
Water Activity	*Aqua Lab Manual*			
Water Activity		**0.409 @ 25.0**		1/10/2013

113365-03	30-4701Loxasperse w/o Desicant@45C+-1C Day90 12/16			
Test	*Method Reference*	***Result***	*Units*	*Analysis Start Date*
Water Activity	*Aqua Lab Manual*			
Water Activity		**0.489 @ 25.0**		1/10/2013

Water activity after 90 days of storage at 3 different temps, without a desiccant.
No microbial growth is possible in the powder

Water Activity of LoxaSperse Powder, with a Desiccant

113365-04 30-4701 Loxasperse w/ Desicant @AmbT Day90 12/16

Test	*Method Reference*	***Result***	*Units*	*Analysis Start Date*
Water Activity	*Aqua Lab Manual*			
Water Activity		**0.321 @ 25.1**		1/10/2013

113365-05 30-4701 Loxasperse w/ Desicant @4C+-1C Day90 12/16

Test	*Method Reference*	***Result***	*Units*	*Analysis Start Date*
Water Activity	*Aqua Lab Manual*			
Water Activity		**0.297 @ 25.3**		1/10/2013

113365-06 30-4701 Loxasperse w/ Desicant@45C+-1C Day90 12/16

Test	*Method Reference*	***Result***	*Units*	*Analysis Start Date*
Water Activity	*Aqua Lab Manual*			
Water Activity		**0.344 @25.4**		1/10/2013

With desiccant, even lower water activity

LoxaSperse Conclusions

- Loxasperse is an innovative powder excipient that:
  - Increases the solubility and dispersability (reduces particle sizes) of imbedded actives
  - Is a low-bioburden, low water-activity powder that is incapable of supporting microbial growth
  - May be synergistic with traditional antimicrobials (as demonstrated in the lowering of MIC for itraconazole)
  - Is a viable base to utilize in the preparation of capsules, for the ultimate purpose of adding the contents of the capsules to sterile water or saline, at the moment of administration, for sinus irrigation.
- Further studies are being completed to evaluate bacterial biofilm disruption, as well as antimicrobial synergy.

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