

CLINITAS SOOTHE

TECHNICAL PRODUCT SUMMARY AND CLINICAL DATA

The Product

Clinitas Soothe contains 0.4% sodium hyaluronate (HA) in a preservative free, and highly purified formulation of pharmaceutical grade purity. Each preservative-free single use container (SUC) contains 0.5 ml of solution in an ergonomically developed moulded container, free from sharp protrusions. The SUCs are provided in strips of 5 with each strip enclosed in a separate aluminium foil pouch. Each pack contains four foil pouches along with an information leaflet.

Clinitas Soothe was developed for chronic use in sensitive eyes and takes advantage of:

- Highest concentration of HA for external ophthalmic use
- All the benefits of HA
- HA produced by fermentation with streptococcus bacillus (complies with Eu Ph)
- Pharmaceutical grade, highly purified HA
- Preservative free
- SUC with no sharp edges after opening

Mechanism of Action

Sodium hyaluronate is the sodium salt of the naturally occurring water soluble polysaccharide found in human connective tissue. It is found naturally in high concentrations within the vitreous of the eye where, together with collagen fibres, it forms the framework of the vitreous humour. The volume of the HA molecule increases from about 0.66 cc/g when dehydrated, to a

hydrated specific volume of 2 to 3000 cc/g showing remarkable water retention properties.¹ Hyaluronic acid is also found in the corneal intercellular spaces without any evidence of binding to collagen fibres.²

The water binding property of HA contributes to some of its other benefits when used as a topical formulation. It improves ocular surface wettability³, and enables it to bind to cell membranes, making it mucoadhesive. The mucoadhesive properties of hyaluronic acid are well known and are now being used in other drug delivery systems such as microspheres.⁴

The viscosity of a substance at rest is a function of concentration, molecular weight, and the size of the flexible polymer units in the material. In solution, sodium HA unfolds and forms a long, loose, randomly arranged coil. With increased concentration, the large molecular coils overlap and become compressed. This increases the viscosity and the elasticity of the solution. At high shear rates, the viscosity is independent of the molecular weight and is determined by the concentration.⁵

Viscoelastics with non-Newtonian (pseudoplastic) properties are viscous at rest but transform to a more liquid-like (less viscous) form at high shear rates. The higher the viscosity of a solution, the greater is the resistance to flow (see Figure 1): solutions with a high viscosity are, therefore, excellent lubricants with a prolonged retention time.

¹ Balazs EA, Denlinger JL: Aging changes in the vitreous. In: Aging and Human Visual Function, pp 45–57. New York, Alan R Liss, 1982

² Cintron C, Covington HI: Proteoglycan distribution in developing rabbit cornea. *J Histochem Cytochem* 38:675, 1990

³ Nakamura M et al. Characterisation of water retentive properties of hyaluronan. *Cornea* 1992;12:433-6

⁴ Lim ST, Martin GP, Berry DJ, Brown MB. Preparation and evaluation of the in vitro drug release properties and mucoadhesion of novel microspheres of **hyaluronic acid** and chitosan. *J Control Release*. 2000;66:281-292.

⁵ Lane SS. Ophthalmic Viscoelastic Devices (OVDs): Physical Characteristics and Clinical Applications. In Duane's Ophthalmology on CD-ROM (2006 edition). Tasman W and Jaeger EA (eds). Lippincott Williams & Wilkins. Vol 6. Ch.9.

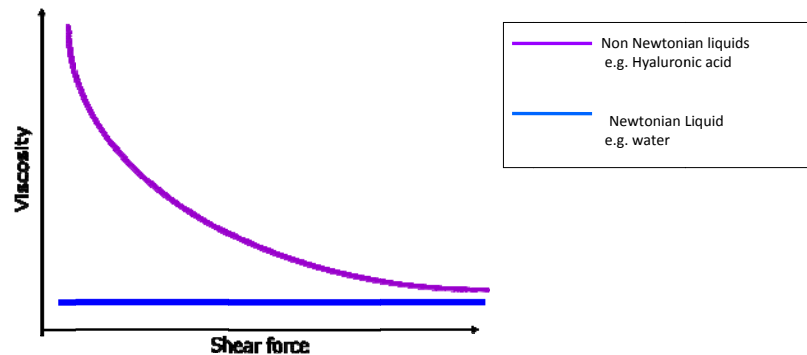


Figure 1. Schematic representation of the change of viscosity with increasing shear force in Newtonian and non-Newtonian liquids.

When used as eye drops, these properties provide an excellent cover for the ocular surface, but this increased viscosity may also impede the movement of the eyelids during blinking and reduce patient tolerance⁶. This is when pseudoplasticity is required. When pseudoplasticity is high, the change from viscous to liquid during a blink is quicker. The relatively high concentration of HA in Clinitas Soothe has been chosen to provide increased viscosity at rest for a longer duration of action, and even better non-Newtonian properties for enhanced comfort during blinking compared to eye drop formulations with lower concentrations of HA.

In order to be defined as “mucomimetic,” an artificial tear must have another characteristic of tears. A recognised test for the mucous quality of tears is the “Tear Ferning Test”. Mannucci *et al* tested 14 different artificial tear preparations including 6 formulations containing HA at different strengths. Of the latter, only unpreserved 0.4% HA in SUC showed clear ferning properties; other HA formulations showed no or incomplete ferning. In the same paper, the authors note that previous work by their group with 0.4% HA demonstrated ferning that was very similar to normal tears.⁷

HA increases the stability of the pre-corneal tear film, and protects the epithelium.⁸ HA facilitates corneal epithelial wound healing in diabetic rats, through, at least in part, the binding

⁶ Dudinski O, Finnin BC, Reed BL. Acceptability of thickened eye drops to human subjects. *Curr Ther Res* 1983;33:322-327.

⁷ Mannucci LL, Fregona I, Mannucci M. Proprietá mucomimetiche deo sostitutivi lacrimali. *EUVISION Superficie Oculare Contattologia, Ipovisione*. 1/04;1-7. 2004.

⁸ Stern ME et al, The pathology of dry eye: the interaction between the ocular surface and lachrymal gland. *Cornea* 1992;11:288-93

to a provisional fibronectin matrix.⁹ In a rabbit *in vivo* model, HA appears to promote corneal epithelial wound healing in a concentration dependent manner with 0.2% and 0.4% being statistically superior to 0%, 0.015% and 0.1% solutions. 0.4% HA solution was numerically superior to 0.2% HA but this failed to reach statistical significance due to the small sample size¹⁰. Superficial punctate keratitis is a common sign in KCS and, when present, is associated with increased discomfort. Gomes et al showed that sodium hyaluronate promotes migration of human corneal epithelial cells *in vitro*.¹¹

Preservatives

Many products used for the relief of dry eye symptoms contain preservatives. The use of preservatives, especially over a long period of time, further aggravates the epithelium.¹² All preservatives have the potential to cause allergic reactions. Thiomersal, in particular, is associated with Giant Papillary Conjunctivitis and is slowly being phased out. Benzalkonium chloride (BAC) is the most commonly used preservative. Frequent use of ophthalmic solutions containing preservatives can cause a higher incidence of epithelial damage, and oedema in patients with glaucoma, dry eyes, infections or iritis, who need to use eye drops for a long period of time. Repeated doses of preserved eye drops can have a cumulative effect, and the prolonged contact with the epithelium may cause chronic irritation and subconjunctival fibrosis. This may increase the risk of failure of trabeculectomy in patients with glaucoma.¹³

Clinitas Soothe is designed to bring these benefits to patients. The SUCs are convenient to use and specifically moulded to prevent the formation of sharp edges after opening. Appendix 1 shows electron microscope images which compare a Clinitas Soothe container with a Blow Fill Seal container in which most products on the market are presented. It offers the highest concentration (0.4%) of HA for products of its kind for excellent rheological properties (Non-Newtonian and viscous solution). These, together with the water binding properties of HA, make it both mucomimetic and mucoadhesive which, in turn, enable it to have a prolonged

⁹ Nakamura M, Sato N, Tai-Ichiro C, Hasegawa, Y, Nishida T. Hyaluronan Facilitates Corneal Epithelial Wound Healing in Diabetic Rats. *Exp Eye Res* 1997;64:1043-1050.

¹⁰ Camilleri G, Bucolo C, Rossi S, Drago F. Hyaluronon-induced Stimulation of Corneal Wound Healing is a Pure Pharmacological Effect. *J Ocul Pharm Ther* 2004;20:548-553.

¹¹ Gomes et al. Sodium hyaluronate (hyaluronic acid) promotes migration of human corneal epithelial cells *in vitro*. *British Journal of Ophthalmology* 2004;**88**:821-825.

¹² Pisella PJ, Pouliquen P and Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol* 2002;86:418-423.

¹³ Noecker R, Ophthalmic Preservatives: Considerations for Long-term Use in Patients With Dry Eye or Glaucoma, *Review of Ophthalmology*, June 2001.

retention time to protect the corneal epithelium and promote its repair. As an unpreserved formulation, it avoids the problems associated with preservatives especially with chronic use and/or contact lens use. All of these benefits contribute to patients' comfort.

Clinical Studies and Information

Non-clinical studies have shown that HA has the ability to enhance corneal epithelial repair. This has a clear advantage in the treatment of dry eye patients who frequently show superficial punctate staining with fluorescein and Rose Bengal stains. Staining is associated with an increased severity of disease and ocular discomfort. Various clinical studies have shown that formulations of HA improve corneal staining.

Yokoi *et al* investigated this by quantifying the amount of fluorescein uptake (using a slit lamp fluorophotometer) in corneas of 10 dry eye patients with corneal staining. Patients were allowed to continue using their normal artificial tears, but had a 0.1% HA eye drop instilled in 1 eye only 1minute after the normal artificial tear drop and every 2 hours during daytime. After two weeks treatment, HA treated eyes showed statistically significant improvement in fluorescein uptake in the inferior region compared to baseline ($p<0.025$). Both inferior and central regions showed significant improvement after 4 weeks treatment ($p<0.025$). There was no improvement in the untreated eyes (Figure 2)¹⁴.

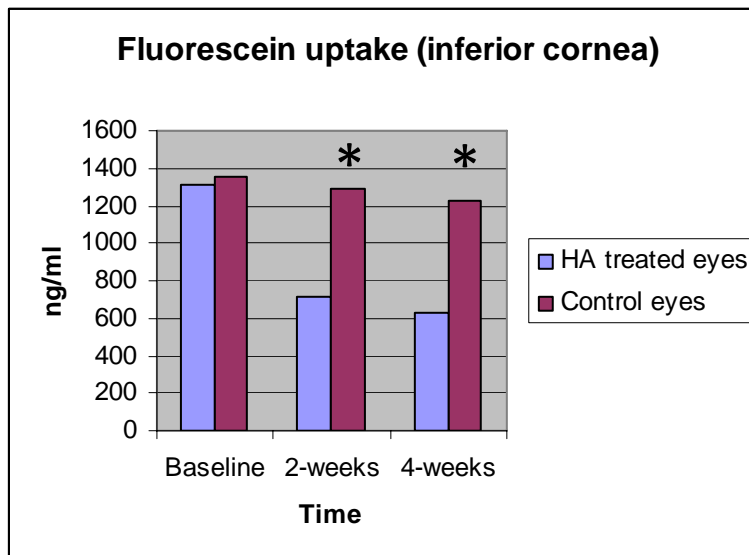


Figure 2. Fluorescein uptake at the inferior corneal region before and after treatment with HA solution. Statistical significance was observed at 2 and 4 weeks after treatment was initiated ($p<0.025$). Adapted from Yokoi *et al*.

¹⁴ Yokoi N, Komuro A, Nishida K, Kinoshita S. Effectiveness of hyaluronan on corneal epithelial barrier function in dry eye. *Br J Ophthalmol* 1997;81:533-536

Long term use (over 3 months) of an HA containing product in humans led to an improvement in the epithelium as assessed using impression cytology.¹⁵ Condon et al also showed an improvement in Rose Bengal staining.¹⁶

Snibson et al¹⁷ investigated ocular residence times, using γ -scintigraphy, for a hyaluronic acid formulation (0.2%) and compared it with 1.4% polyvinyl alcohol (PVA, Liquifilm® Tears, Allergan), and 0.3% hydropropylmethylcellulose (HPMC, Hypromellose). Six subjects with well documented keratoconjunctivitis sicca (KCS), which necessitated frequent use of artificial tears, were randomised to receive each of the three formulations in one of six sequences. A washout of the previous dry eye treatment of ≥ 6 hours was required, and the interval between the use of test materials was 5 days apart to ensure complete elimination of isotope.

Data was reported from 5 patients. HPMC and PVA were found to clear more rapidly than the HA solution during the first 15 minutes after instillation. The time for half of the radiolabeled ophthalmic solution to be cleared from the ocular surface (T_{50}) was calculated from the individual curve-fit plots. The Mean T_{50} (SD) for the HA solution was 321 (149) seconds compared with 44 (25) and 39 (7) seconds for the HPMC and PVA formulations respectively (Figure 3). This difference between the HA solution and the comparators was statistical significant ($p=0.012$ vs. HPMC and $p=0.013$ vs. PVA). The area under the curve for corneal clearance for HA was significantly greater than that for PVA ($p=0.028$) and showed trend against HPMC ($p=0.057$).

¹⁵ Aragona P et al, Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients. Br J Ophthalmol 2002;86:181-184

¹⁶ Condon PI et al, Double blind, randomised, placebo controlled, crossover multicentre study to determine the efficacy of a 0.1% (w/v) sodium hyaluronate solution (Fermavisc) in the treatment of dry eye syndrome. Br J Ophthalmol 1999;83:1121-4.

¹⁷ Snibson GR, Greaves JL, Soper NDW, Tiffany JM, Wilson CG, Bron AJ. Ocular Residence Times of Artificial Tear Solutions. Cornea 1992; 11:288-293.

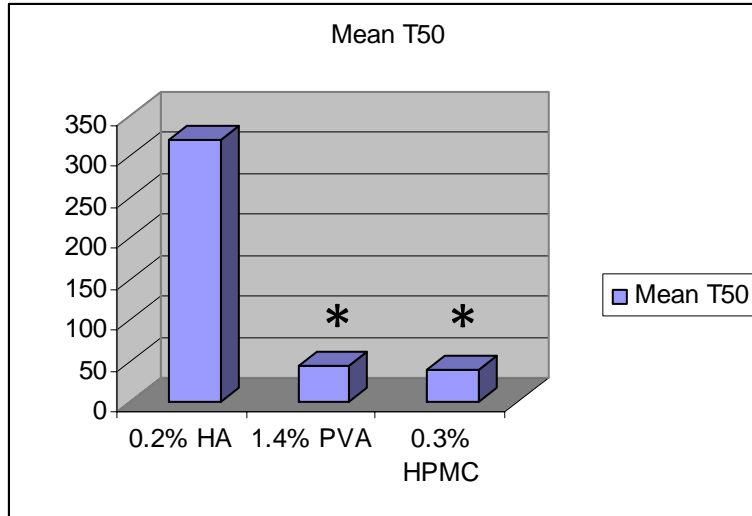


Figure 3. Mean time (s) for half of the radiolabeled ophthalmic solution to be cleared from the ocular surface of subjects with KCS (T₅₀). Adapted from Snibson *et al* (1992).

The authors also noted that in another study conducted by their group, 0.2% and 0.3% HA solutions were compared to a normal buffered saline solution in both normal subjects and KCS patients. The HA solutions were found to have prolonged ocular residence times in both groups, although the retention times in KCS patients was significantly longer than in normal subjects¹⁸. This study demonstrated that, using mean T₅₀ as an indicator of residence time, 0.2% HA solution persists 7 times longer than longer formulations of PVA or HPMC commonly used to treat KCS patients.

¹⁸ Snibson GR, Greaves JL, Soper NDW, Prydal JI, Wilson CG, Bron AJ. Precorneal residence times of sodium hyaluronate solutions studies by quantitative gamma scintigraphy. *Eye* 1990;4:594-602.

Garza-Saide *et al* conducted an investigator masked, prospective randomised, cross over study in 20 patients with dry eye to compare the safety and efficacy of a preservative free formulation of 0.4% hyaluronic acid with a 0.2% polyacrylic liquid gel formulation. Both products were used three times daily for 28 days. Both formulations were effective compared to baseline with respect to signs and symptoms. There was no statistically significant difference between the 2 preparations except with respect to Non-Invasive Tear Break Up Time: this was significantly longer for the HA formulation. Although the detail provided in this poster abstract is insufficient to appreciate the severity of the disease treated, it provides further support to the findings of Snibson *et al* described above, especially considering that polyacrylic acid also has a high viscosity and non-Newtonian properties¹⁹.

In a multicentre study²⁰, 135 consecutive patients with moderate to severe Kerato-Conjunctivitis Sicca (KCS) were randomised to receive either 0.4% HA solution or 0.3% Hydroxymethylcellulose/ 0.1% dextran (HPMC) eye drops 6 times daily. All subjects were assessed for at least 60 days; impression cytology was done on day 90 on a subgroup of patients. There were no significant differences for signs and symptoms between the groups at baseline.

Information was recorded for the key symptoms (foreign body sensation, burning, pain and photophobia) and signs (staining with fluorescein and Rose Bengal, Schirmer's Test I, and Tear Break up Time) at baseline (obtained after 5 days' washout using normal saline) and on days 15, 30 and 60. Both treatments provided a statistically significant improvement in all signs and symptoms by the end of the treatment period, day 60. In addition, a significant difference was found, favouring 0.4% HA for all signs and symptoms at every post-baseline visit.

Other investigations such as tear ferning test (day 60), and impression cytology (day 90) also showed a significant improvement over baseline with the 0.4% HA solution. These results are summarised in Table 1.

Based on these results, the authors conclude that the 0.4% HA formulation tested resulted in an improvement in the epithelial condition of the ocular surface and a superior benefit for the patients with respect to symptoms and signs.

¹⁹ Garza-Saide O, Lozano-López LA, Padilla-Morones M, López-Chávez E. Hyaluronic Acid 0.4% Preservative Free, an humectant for the Treatment of Dry Eye: A Comparative Clinical Trial of Safety and Efficacy vs. Polyacrylic Acid 0.2% Liquid Gel. Poster Presented at 3rd International Symposium of Ocular Pharmacology and Pharmaceutics (ISOPP), Lisbon, Portugal, February 10-13, 2000.

²⁰ Iester M, Orsoni GJ, Gamba G, Taffara M, Mangiafico P, Guiffrida S, Rolando M. Improvement of the ocular surface using hypotonic 0.4% hyaluronic acid drops in keratoconjunctivitis sicca. *Eye* 2000; 14:892-898.

Symptom or sign	n(eyes) 0.4% HA/ 0.3% HPMC	Summary of result differences
Photophobia	116/110	Both groups showed statistically significant difference vs. baseline at day 60. 0.4% HA statistically superior to 0.3% HPMC on days 15, 30 and 60.
Pain		
Burning		
Foreign Body Sensation		
Fluorescein staining		Both groups showed statistically significant difference vs. baseline at day 60. 0.4% HA statistically superior to 0.3% HPMC on days 15, 30 and 60.
Rose Bengal staining		
Schirmer's I test		
Tear Break Up Time		
Ferning test	30/32	Both groups showed statistically significant difference vs. baseline at day 60 both at 30 and 90 minutes after the last instillation. 0.4% HA was statistically superior to HPMC on day 60, 30 minutes after last instillation.
Impression Cytology	28/22	0.4% HA was statistically superior to HPMC and compared with baseline on day 90.

Table 1 Summary table for key results in a clinical study comparing 0.4% Hyaluronic acid and 0.3% hydroxymethylcellulose/0.1% dextran eye drop solutions.

It is important to note that the benefits to patients may outlast the clearance of a product. Thus, in a clinical study on 10 patients, Mengher *et al* using a non-invasive assessment of tear film breakup time (NIBUT), 0.1% HA solution was shown to enhance tear film stability in patients with dry eye for >40 minutes, with an effect on symptoms lasting up to 1 hour.²¹ Clearance of a product from the corneal surface is therefore likely to underestimate the duration of the effect on the stabilisation of the tear film.

In a study of 22 patients²² with moderate dry eye with superficial keratitis, when compared with carboxymethylcellulose (CMC, Carmellose) using corneal staining, flow cytometry analysis and impression cytology, recovery in keratitis (type, extent and depth) and symptoms resolved faster in the sodium hyaluronate group than in the CMC group. The study concluded that sodium hyaluronate was well tolerated and tended to show a faster efficacy than did the CMC-based formulation in patients with moderate dry eye and superficial keratitis. The authors recommended sodium hyaluronate as being advantageous and should be considered in treating early stages of dry eye.

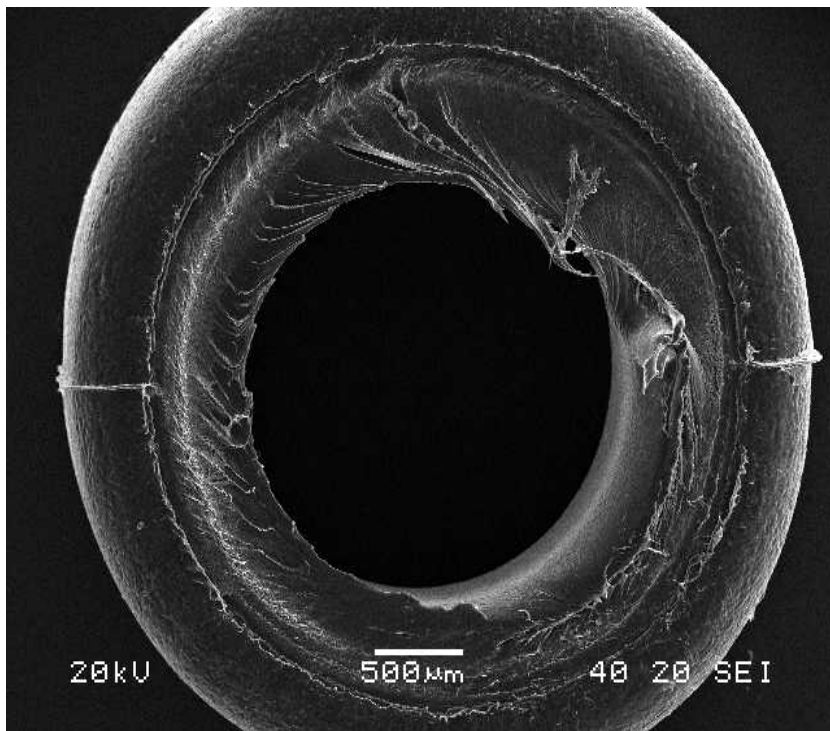
Conclusion

Clinitas Soothe contains sodium hyaluronate, a lubricant that has been used in ophthalmic surgery for some years but is now being acknowledged as having a useful role to play in dry eye. The concentration of sodium hyaluronate, at 0.4% is the highest available and this along with the optimised molecular weight results in a product with properties that are balanced between comfort and high viscosity. In addition, the lack of preservative makes the product particularly suitable for chronic use.

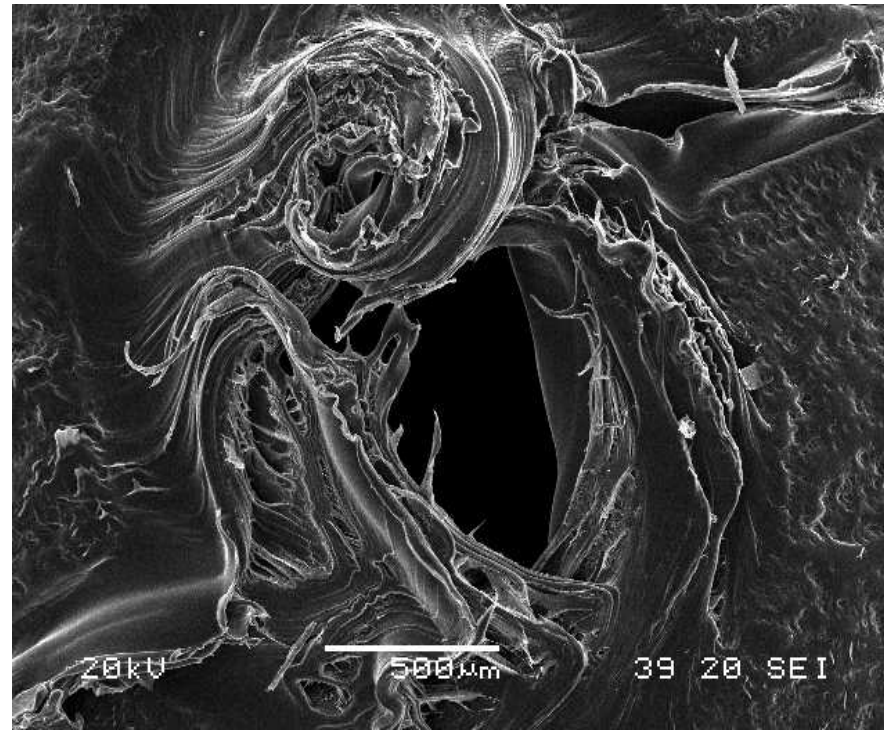
²¹ Mengher LS, Pandher KS, Bron AJ, Davey CC. The effect of sodium hyaluronate (0.1%) on break up time (NIBUT) in patients with dry eyes. *Br J Ophthalmol* 1986;70:442-447.

²² Brignole F, Piscella PJ, Dupas B, Baeyens V and Baudouin C. Efficacy and safety of 0.18% sodium hyaluronate in patients with moderate dry eye syndrome and superficial keratitis. *Graef. Arch. Clin. Exp.Ophth.* 2005 243 (6) 531-8

Appendix 1: Comparison of Clinitas Soothe Container with Blow Fill Seal Container



Electron microscope image of tip of Clinitas Soothe SUC (single unit container)



Electron microscope image of tip of Blow Fill Seal container utilised for most single use products.