

CLINITAS HYDRATE

TECHNICAL PRODUCT SUMMARY AND CLINICAL DATA

The Product

Clinitas Hydrate contains carbomer 980¹, which is a synthetic high molecular weight cross-linked polymer of acrylic acid which gives a high viscosity gel. Clinitas hydrate is a liquid gel formulated to produce a transparent, lubricating film covering the cornea and conjunctiva. The product also contains a preservative, cetrimide, thus avoiding the well known problems associated with the use of benzalkonium chloride. Carbomers combine several physical characteristics such as long residence time and non-Newtonian properties that are beneficial to patients with symptoms typically caused by an unstable or deficient tear film.

Mechanism of Action

Carbomer 980 is a cross linked polyacrylate polymer with a molecular weight ranging from 700 000 to 3 or 4 billion, but there are no methods for measuring the molecular weights of three-dimensional polymers of this type. It forms a network structure of polymer chains interconnected by crosslinks. They swell in water up to 1000 times their original volume to form a gel. Carbomer polymer microgels are easily moved by shear but once the shear stops, the macrogel structure immediately forms again.² It offers properties that are similar to those of carbomer 940. A 0.2% neutralized solution of carbomer 980 has a viscosity range of 13,000 – 30,000 mPa.s.³ Carbomer 980 is preferred over carbomer 940

¹ n.b. The name Carbopol® is often used in literature. This is the trade name for carbomer registered and owned by The Lubrizol Corporation. Other generic names include, “polyacrylic acid”, “carboxyvinyl polymer” and “carboxy polymethylene” depending on the pharmacopoeia being used.

² Anonymous. Nomenclature and Chemistry. Noveon Pharmaceutical Polymers. Bulletin 3. January 2002.

³ Lubrizol Advanced Materials Inc. Carbopol® 980, 981, 2984 & 5984 Polymers. Product Specifications. Edition February, 2001.

since it is polymerized in a cosolvent system so that it contains no residual benzene.⁴ In a rabbit study, Carbomer 980 was found to be non-irritant to eyes.⁵

Mucoadhesion is the ability of a material to “stick” to a mucous membrane, resulting in a protracted contact time. To do so, the material must interact with the mucus, which is a highly hydrated, viscous anionic hydrogel layer protecting the mucosa. Mucin is composed largely of flexible glycoprotein chains. Generally, polyacrylic acid polymers are understood to interact with the mucin by means of hydrogen bonds, resulting in adhesion of the polymer to the mucin, although the exact mechanism is not yet fully understood. Whatever the mechanism, once adhered, the carbomer polymer based vehicle is highly resistant to being washed away.⁶

Polyacrylic acid possesses excellent mucoadhesive properties.⁷ This, along with its liquid gel properties, enable to have a relatively prolonged retention time on the ocular surface. In a rabbit study, Carbopol 934P was found to have a significantly greater precorneal retention time compared with polyvinyl alcohol.⁸

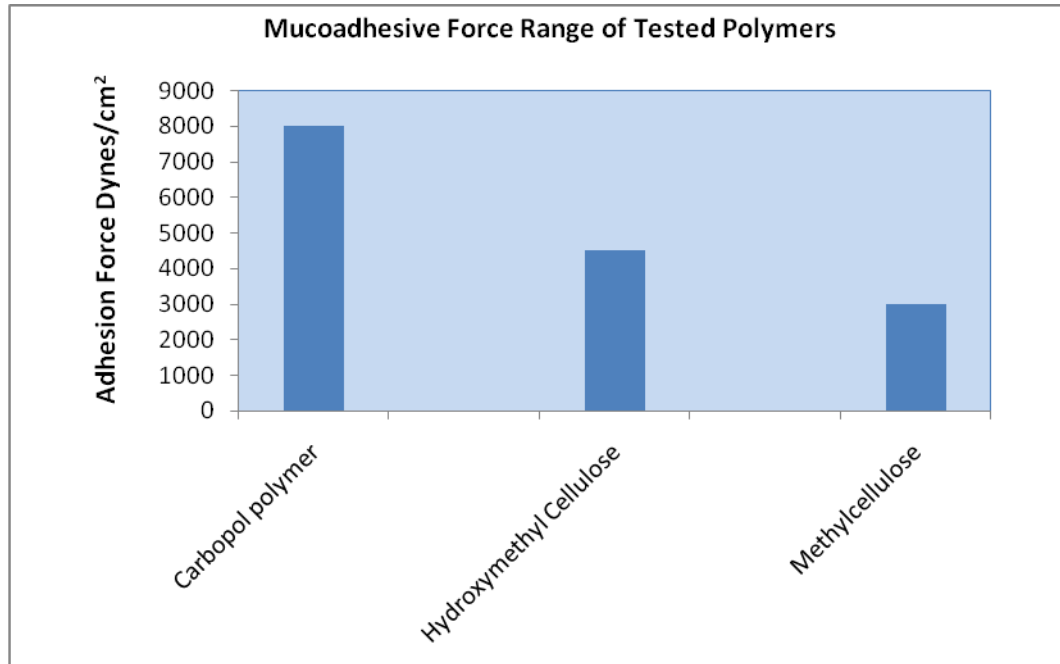
⁴ Lubrizol Advanced Materials Inc. Carbopol® 934, 940 & 941 Polymers. Product Specifications. Edition July 17, 1997.

⁵ Lubrizol Advanced Materials Inc. Carbopol® 980 and 981 Polymer toxicology Studies. Edition August 1, 2003.

⁶ Anonymous. Bioadhesion. Noveon Pharmaceutical Polymers. Noveon Pharmaceutical Polymers. Bulletin 16. January 2002.

⁷ Smart, J.D., “Some Formulation Factors Influencing the Rate of Drug Release from Bioadhesive Matrices,” Drug Devel. Ind. Pharm., 18(2), 223-232, 1992

⁸ Davies NM, Farr SJ, Hadgraft J, Kellaway IW. Evaluation of mucoadhesive polymers in ocular drug delivery. I. Viscous solutions. Pharm Res 1991;8:1039-1043. Abstract.



Extracted from Smart et al, 1992

Clinitas hydrate is formulated as a liquid gel preserved with cetrimide. Although the product is presented in a tube, unlike an ointment, a single drop can easily be administered to each eye without needing to squeeze the tube. Indeed, the squeezing of the tube is not advisable as this would lead to an excessive amount being administered with waste and increased blurring.

The use of cetrimide avoids the need for benzalkonium chloride and thus some of its well known toxicity to the ocular surface. In an *in vitro* comparison of several ophthalmic lubricating eye drops, cetrimide was found to be less cytotoxic than phenylmercury and BAK 0.01%.⁹ It is noteworthy that Debbasch et al following an *in vitro* assessment conclude that, carbomers possess antioxidant properties and tend to reduce the toxic effects of preservatives.¹⁰

⁹ Noecker RJ. Purote May be Gentler Preservative for Lubrication Solutions. *Ophthalmol Times* 2001; November 1.

¹⁰ Debbasch C, Bruneau De La Salle S, Brignole F, Rat P, et al. Cytoprotective effects of Hyaluronic Acid and Carbomer 934P in Ocular Surface Epithelial Cells. *Invest Ophthalmol Vis Sci* 2002;43:3409-3415.

Clinical Studies and Information

Carbomers possess excellent mucoadhesive properties, an increased viscosity with non-Newtonian characteristics. These property give improved ocular residence times compared to most older lubricating products. Marquardt and Christ conducted a study in 30 healthy subjects comparing a carbomer formulation to another tear solution based on polyvinyl alcohol. The carbomer based solution showed an ocular residence time 7 times longer than the comparator. In a second study including 7 normal subjects and 5 patients with keratoconjunctivitis sicca, the effect of the carbomer based product on break-up time (BUT) and the Schirmer test was demonstrated. It was found that tear secretion improved for 2-4 hours (Schirmer test) and the stability of the tear film (BUT) improved for about 6 hours after instillation of the product.¹¹

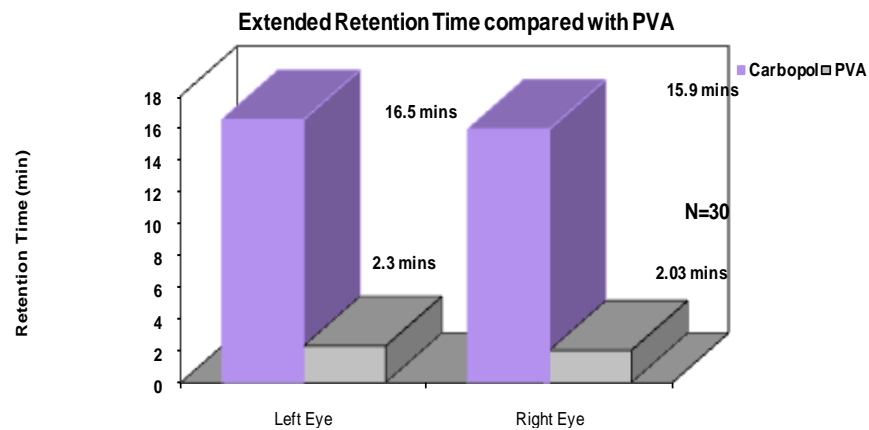


Figure 1 Comparison of Retention Times.¹¹

¹¹ Marquardt R, Christ T. [Contact Time of Artificial Tear Solutions] *Klin Monatsbl Augenheilkd* 1986;189:254-257. Abstract. Original in German.

Wilson et al, used radiolabelled carbomer in healthy volunteers to assess retention time. Their data demonstrated that carbomer based gels significantly extend the contact time of solutes or suspended solids with the corneal surface. Eight minutes post dosing, over 40% of the gel was retained compared with 7% of the saline control. At 10 minutes after instillation, the retention of the labelled gel, as measured from the solute or particulate phase marker, shows more than 40% of the label was associated with the cornea. At 35 minutes, approximately 20% of the activity is associated with the cornea, suggesting stabilisation of tear film for a considerable time.¹²

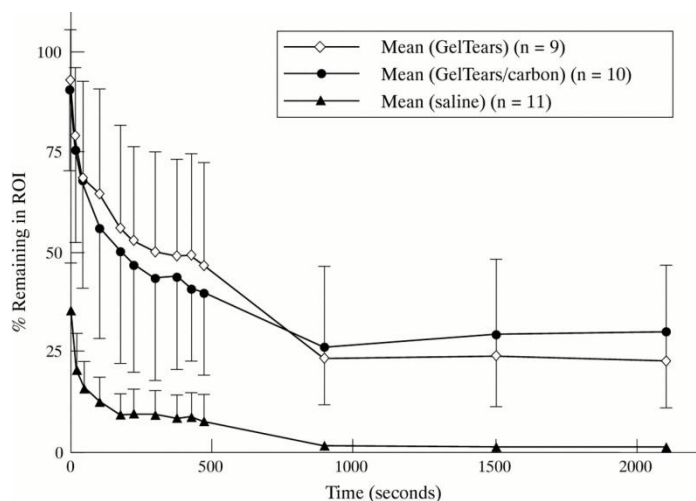


Figure 2. Mean corneal clearance of GelTears or saline formulations labelled with ^{99m}Tc-DTPA in the solution or particulate phase (mean (SD)).¹²

Al-Mansouri et al also compared a carbomer vs. a polyvinyl alcohol solution in a right eye vs. left eye controlled study. They included 20 healthy subjects and 20 patients with dry eye. In healthy subjects,

¹² Wilson, C. G, Zhu YP, Frier M, Rao LS et al. Ocular contact time of a carbomer gel (GelTears) in humans. *Br J Ophthalmol* 1998;82:1131-1134

corneal residence time averaged 36.5 (± 14.2) minutes for the carbomer formulation compared with 19.5 (± 8.3) minutes for the polyvinyl alcohol formulation. These times were even longer in dry patients at 92.8 min (± 35.7) and 40.8 min (± 19.4) for the carbomer and PVA treated eyes respectively. Tear Break-up-Time in healthy subjects was 26.2 (± 4.4) seconds for the carbomer solution compared with 16.5 seconds (± 7.1) for the polyvinyl alcohol product. In dry subjects, these were 23.0 seconds (± 5.5) and 10.4 seconds (± 3.4) for the carbomer and PVA treated eyes respectively. The difference in Tear Break up Time was statistically significantly better ($p < 0.001$). 75% of dry eye patients preferred the carbomer based product.¹³

Sullivan, L. J. et al., undertook a multicenter, single-blind, randomised, placebo-controlled study on 123 patients with moderate-to-severe dry eye to assess the efficacy and safety of carbomer gel. All primary subjective symptoms (discomfort, dryness and foreign body sensation) decreased significantly and the objective parameter (rose Bengal staining) improved in the carbomer gel-treated group compared to the placebo group. The data showed a statistically significant difference from placebo by day 10 for severe dry eye disease and by 42 for moderate disease. These results suggested that the carbomer gel may be of most benefit for the more severely affected patients with dry eye. The gel was also statistically superior to placebo for other subjective symptoms, such as tearing, itching, scaling or conjunctival discharge. The results also indicated that carbomer gel was as safe as placebo.¹⁴

In a randomized, multicentre crossover study by Marner et al, the efficacy and safety of a carbomer containing ocular gel was compared to a commonly used 1.4% polyvinyl alcohol-based (PVA) artificial tear preparation, both used for a 2-week period. 61 patients were treated. A statistically significant difference in favour of the new viscous carbomer eye gel compared to the PVA preparation was achieved in reducing the symptom of dryness, the total symptom score and prolongation of the tear break-up time. During the carbomer eye drops period the mean daily frequency of application was 3.92 compared to 4.64 for the PVA eye drops period ($p = 0.02$). More patients had noted transient blurred vision with the carbomer gel.¹⁵

¹³ al-Mansouri S, Tabbara KF, Rask-Pedersen E. Lubrithal (Leo viscous eye gel), precorneal residence time in normal and dry eyes. *Doc Ophthalmol* 1994;88:187-194.

¹⁴ Sullivan-L-J, McCurrach-F, Lee-S, Taylor-H-R,, et al.. Efficacy and Safety of 0.3% carbomer gel compared to placebo in patients with moderate-to-severe dry eye syndrome. *Ophthalmol* 1997;104:1402-1408.

¹⁵ Marner-K, Mooller-P-M, Dillon-M, Rask-Pedersen-E. Viscous carbomer eye drops in patients with dry eyes. Efficacy and Safety. A randomized, open, cross-over, multicentre study. *Acta-Ophthalmol-Scand* 1996;74:249-252.

These results are supported by the work of Brodwall et al.¹⁶ In a prospective, randomized, single-masked study comparing a carbomer gel 0.2% to polyvinyl alcohol 1.4% (n= 43 and 42, respectively) in patients with dry eye, they found that the reduction in total symptoms (gritty or foreign body sensation, burning sensation, dry eye sensation, photophobia, others) and signs (conjunctival hyperaemia, ciliary injection, corneal and conjunctival epithelial staining) score on carbomer therapy was significantly greater than that on PVA at both two and four weeks. The daily frequency of instillation of the carbomer was significantly less than that of PVA on 16 of the 27 (59%) study days. Both prescribers and patients preferred the carbomer liquid gel product.

Bron et al¹⁷ provided further evidence of the superior efficacy of carbomer gels over PVA products. Eighty-nine patients with dry eyes were randomly allocated to treatment with either carbomer (n = 48) or PVA (n = 41) in a prospective, investigator-masked study in two centres. The parameters assessed were daily frequency of instillation of the study medications, ocular signs and symptoms, tear film break up time, Schirmer's test values, local tolerance and global assessment of the improvement following treatment. The two groups were similar in patient demographics and study parameters at baseline. The total score of symptoms (gritty or foreign body sensation, burning sensation, dry eye sensation, photophobia, others) and signs (conjunctival hyperaemia, ciliary injection, corneal and conjunctival epithelial staining) was reduced significantly more by treatment with the carbomer gel than with PVA at both three and six weeks ($p < 0.0001$). The daily frequency of instillation of the carbomer based product was significantly less than that PVA on 38 of the 41 (93%) study days. Both test and comparator products were safe and were equally well-tolerated except for blurred vision, usually mild and transient, on carbomer. On global assessment of the improvement in their dry eye condition, significantly more carbomer treated patients felt better on treatment at six ($p = 0.02$) weeks compared with those on PVA. They concluded that carbomer gel was as safe as, and more effective than polyvinylalcohol in the treatment of patients with dry eyes.

Interestingly, this reduction in frequency of application was found to be statistically significant in a comparative study against drops containing chondroitin sulphate. In a randomised, open labeled multicentre study, Laroche et al also found better efficacy on the symptoms as well as on the objective

¹⁶ Brodwall J, Alme G, Gedde-Dahl S, Smith J et al. A Comparative study of polyacrylic acid (Viscotears) liquid gel versus polyvinylalcohol in the treatment of dry eyes. *Acta Ophthalmol Scand* 1997;75:457-461.

¹⁷ Bron AJ, Mangat H, Quinlan M, Foley-Nolan A et al. Polyacrylic acid gel in patients with dry eyes: a randomised comparison with polyvinyl alcohol. *Eur J Ophthalmol* 1998;Apr-Jun:8:81-9.

criteria (biomicroscopic examination, break-up time, rose Bengal test) for the carbomer product and 81% of the patients were prepared to continue using the carbomer gel compared with 54% for the chondroitin sulphate product.¹⁸

In all the studies above, carbomer gels were found to be well tolerated. The most frequent complaint is a transient blurring of vision immediately after instillation. Most patients accept this without difficulty knowing that after a few blinks, the drop is evenly spread across the ocular surface and normal vision is restored.

Conclusion

In conclusion, the above studies show that the components of Clinitas Hydrate have advantages in clinical use. These include prolonged residence time on the ocular surface, improvement of tear film quality, reduced number of applications required per day and with it a higher compliance and excellent tolerance.

¹⁸ Laroche L, Arrata M, Brasseur G, Lagoutte F et al. Treatment of dry eye syndrome with lacrimal gel: a randomized multicentre study] J Fr Ophthalmol 1991;14:321-326. Abstract.