formulating elegant liquid and semisolid drug products

natrosol™ 250
hydroxyethylcellulose (HEC)

Ashland™
always solving

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contents

introduction

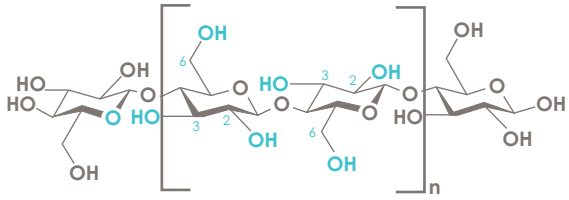
Natrosol™ 250 Pharm hydroxyethylcellulose (HEC) is a nonionic, water-soluble polymer widely used in pharmaceutical formulations. Like Aqualon™ and Blanose™ sodium carboxymethylcellulose (CMC), it is a cellulose ether, but it differs in that it is nonionic and its solutions are unaffected by cations and, thus, less affected by pH changes and more tolerant of the presence of anions and organic co-solvents. It also differs from other cellulose ethers, such as Klucel™ hydroxypropylcellulose (HPC) and Benecel™ hydroxypropylmethylcellulose (HPMC), in that it is soluble in both cold and hot water and does not precipitate from aqueous solutions at elevated temperatures.

This brochure describes the properties of Natrosol™ 250 Pharm HEC and its solutions. Natrosol™ 250 Pharm HEC is a versatile pharmaceutical excipient with many applications including as a tablet binder, a modified-release matrix former, a film-coating agent, and a viscosity modifier. In this brochure we describe the properties and applications of Natrosol™ 250 Pharm HEC in semi-solid and liquid pharmaceutical formulations.

polymer chemistry

The Natrosol™ 250 Pharm HEC polymer is a partially substituted poly(hydroxyethyl) ether of cellulose. The base of the HEC molecule is formed by the polysaccharide cellulose and its β (1→4)–linked D-glucose units. The structure of the cellulose molecule can be visualized as a polymer chain composed of repeating cellobiose units. These, in turn, are composed of two anhydroglucose units (β-glucopyranose residues). Each anhydroglucose unit contains three hydroxyls capable of reaction, shown in light blue in figure 1.

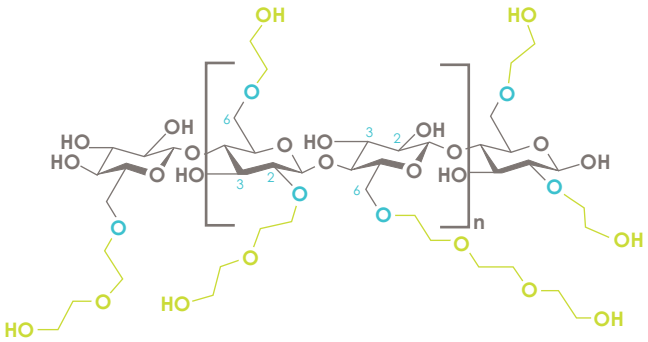
figure 1: Structure of cellulose in chair form notation.



The number of hydroxyl groups substituted per anhydroglucose unit in any reaction is known as the degree of substitution, or DS. Theoretically, all three hydroxyls can be substituted. If all three hydroxyls are replaced, the maximum theoretical D.S. of 3.0 (impossible in practice) would result. By treating cellulose with sodium hydroxide and reacting with ethylene oxide, hydroxyethyl groups are introduced to yield a hydroxyethyl ether. The reaction product is purified and ground to a white to light tan, free-flowing powder. Substitution can also occur when ethylene oxide reacts at previously substituted hydroxyls, and polymerizes to form a side chain (branching). The average number of moles of ethylene oxide that become attached to each anhydroglucose unit in cellulose, in the two ways described, are called total molar substitution, or MS.

In reacting ethylene oxide with cellulose to form the hydroxyethyl ether of cellulose, solubility in water is achieved as the degree of substitution is increased. By selecting appropriate reaction conditions and moles of substituent, complete and quick solubility in water is obtained. Natrosol™ 250 Pharm HEC, which has optimum solubility in water, has a MS of 2.5. An idealized structure of Natrosol™ 250 Pharm HEC is shown in figure 2. This example has a MS of 2.5 (10 ethylene oxide groups/4 anhydroglucose units) and a DS of 1.5 (6 hydroxyls substituted/4 anhydroglucose units).

figure 2: Idealized structure of Natrosol™ 250 Pharm HEC. This example has a MS of 2.5 (10 ethylene oxide groups/4 anhydroglucose units) and a DS of 1.5 (6 hydroxyls substituted/4 anhydroglucose units).



grades and specifications

products available

Natrosol™ 250 Pharm hydroxyethyl cellulose (HEC) is available in several grades as given in table 1. The available grades differ principally in their weight average molecular weight, and thus, in their viscosities measured in aqueous solutions. Additionally, different particle sizes are available to optimize the performance in specific applications, such as the use as matrix former for modified release tablets Natrosol™ 250 Pharm HEC uses a maximum of 1% phosphates as a pH stabilizer.

table 1: Different grades of Natrosol™ 250 Pharm HEC grades. (X = fine grade and W = superfine grade).

	Brookfield viscosity*			
grade	**weight average molecular weight (Da)**	**Brookfield LVF viscosity at 25 °C, mPa·s**	**solution concentration**	**EP viscosity label** at 10^{s-1} and 25 °C (mPa·s in 2% solution)**
natrosol™ 250 L pharm	90,000	75–150	5%	9.5 (at 100^{s-1})
natrosol™ 250 G pharm	300,000	250–400	2%	295
natrosol™ 250 M pharm	720,000	4,500–6,500	2%	4,400
natrosol™ 250 H pharm	1,000,000	1,500–2,500	1%	8,500
natrosol™ 250 HX pharm	1,000,000	1,500–2,500	1%	8,500
natrosol™ 250 HHX pharm	1,300,000	3,500–5,500	1%	14,500
natrosol™ 250 HHW pharm	1,300,000	3,500–5,500	1%	14,500

*Brookfield LV viscosity at 25 °C, mPa·s, according to the Ashland method
**EP label viscosity based on the EP viscosity method. EP viscosity range 75–140% of the value stated on the label (NF viscosity range 50–150% of the value stated on the label).

pharmacopeial specifications

Excipient grades of Natrosol™ 250 Pharm HEC meet the monograph requirements as set forth in the current editions of the United States National Formulary (NF) and the European Pharmacopoeia (Ph. Eur.) The pharmacopeial specifications and Ashland's product specifications are listed in table 2. For pH stabilization of Natrosol™ 250 Pharm HEC a certain amount of phosphate is added. Added phosphate quantity is printed on the bag label.

table 2: Pharmacopeial specifications for hydroxyethylcellulose and compendial compliance of Natrosol™ 250 Pharm HEC.

test	Ph. Eur. 9.0	USP40-NF35	Ashland specification
residue on ignition (calculated as Na_2SO_4, %)			
• natrosol™ 250 G pharm and natrosol™ 250 L pharm* HEC	4.0 max	5.0 max	4.0 max
• all other grades	4.0 max	—	1.0 max
pH, 1% solution	5.5–8.5	6.0–8.5	6.0–8.5
loss on drying, %	10.0 max	10.0 max	5.0 max
nitrate, %			
• natrosol™ 250 G pharm and natrosol™ 250 L pharm* HEC	3.0 max	—	3.0 max
• all other grades	0.2 max	—	0.2 max
chlorides, %	1.0 max	—	0.2 max
heavy metals (as lead), ppm	20 max	20 max	10 max
lead, ppm	—	10 max	0.5 max
arsenic, ppm	—	—	3 max
glyoxal, ppm	20 max	—	20 max
ethylene oxide, ppm	1 max	—	1 max
2-chloroethanol, ppm	10 max	—	10 max

*Low molecular weight HEC with an apparent viscosity of 1000 mPa·s (2% w/v) or less.

Natrosol™ 250 HEC Pharm grades meet the monograph requirements of the United States National Formulary (NF) and the European Pharmacopoeia (Ph. Eur.).

polymer properties

typical properties

table 3: Typical properties for Natrosol™ 250 Pharm hydroxyethylcellulose.

property	value
acidity/alkalinity	pH 6.0 – 8.5 for a 1% w/v aqueous solution
density (bulk)	0.4 – 0.6 g/cm³
density (tap)	0.6 – 0.7 g/cm³
moisture content	≤ 5% (w/w) of water
particle size distribution	standard grind, retained on #40 mesh (420 µm; max 10%) X-grind, retained on #60 mesh (250 µm; max 0.5%) type HHW, retained on #80 mesh (177 µm; max 0.5%)

table 4: Surface tension of different Natrosol™ 250 Pharm HEC grades at varying concentrations and temperatures.

	surface tension (dyne/cm or mN/m) at					
	0.001% (w/v) solution		0.01% (w/v) solution		0.1% (w/v) solution	
grade	at 20 °C	at 25 °C	at 20 °C	at 25 °C	at 20 °C	at 25 °C
natrosol™ 250 L pharm HEC	68.7	70.1	68.2	67.9	65.5	66.5
natrosol™ 250 G pharm HEC	69.2	72.1	67.3	70.7	65.9	70.9
natrosol™ 250 M pharm HEC	69.7	69.6	67	68.9	67.9	70.7
natrosol™ 250 H pharm HEC	67.7	71.1	67.1	69.7	68.1	72.2
natrosol™ 250 HX pharm HEC	67.7	71.1	67.1	69.7	68.1	72.2
natrosol™ 250 HHX pharm HEC	67.8	72.7	67.4	71.8	68.7	73.9

solubility in water and organic solvents

Natrosol™ 250 Pharm HEC dissolves quickly in cold or hot water to form clear and smooth solutions; furthermore, it does not gel or precipitate even when heated to the boiling point of water. Natrosol™ 250 Pharm HEC is essentially insoluble in organic solvents. It is, however, partly soluble in some solvents, usually those that are miscible with water (e.g., ethanol: water mixtures), or that contain polar groups (e.g., glycerin and propylene glycol at temperatures around 55 °C to 60 °C).

The most important uses of Natrosol™ 250 Pharm HEC involve its aqueous solutions — it is soluble in both hot and cold water.

moisture absorption

Natrosol™ 250 Pharm HEC can absorb moisture from the atmosphere, as do other hygroscopic or finely divided materials. The amount of moisture absorbed depends on the initial moisture content of Natrosol™ 250 Pharm HEC and on the relative humidity of the surrounding air. Opened bags not totally used may experience moisture uptake.

The moisture content of Natrosol™ 250 Pharm HEC, when packed by Ashland, does not exceed 5% by weight. During prolonged storage, the moisture content of Natrosol™ 250 Pharm HEC reaches an equilibrium level that varies with temperature and the humidity of the surrounding atmosphere, particularly after the bag is opened.

equilibrium moisture content of Natrosol™ 250 Pharm HEC at 25 °C:

at 50% relative humidity	8.7 ± 0.1% (w/w)
at 90% relative humidity	50.0 ± 2.0% (w/w)

equilibrium moisture content of Natrosol™ 250 Pharm HEC at 40 °C:

at 50% relative humidity	7.8 ± 0.3% (w/w)
at 90% relative humidity	41.0 ± 1.5% (w/w)

To maintain its original moisture content, Natrosol™ 250 Pharm HEC should be stored in tightly closed containers in a dry atmosphere. If stored in open containers, the moisture content will change to an equilibrium value determined by the relative humidity of the environment. The effects of relative humidity on equilibrium moisture contents of different grades of Natrosol™ 250 Pharm HEC at 25 °C (left) and 40 °C are shown in figure 3.

figure 3a: Equilibrium moisture content of different grades of Natrosol™ HEC at 25 °C. The bold lines indicate sorption and dotted lines indicate desorption behavior.

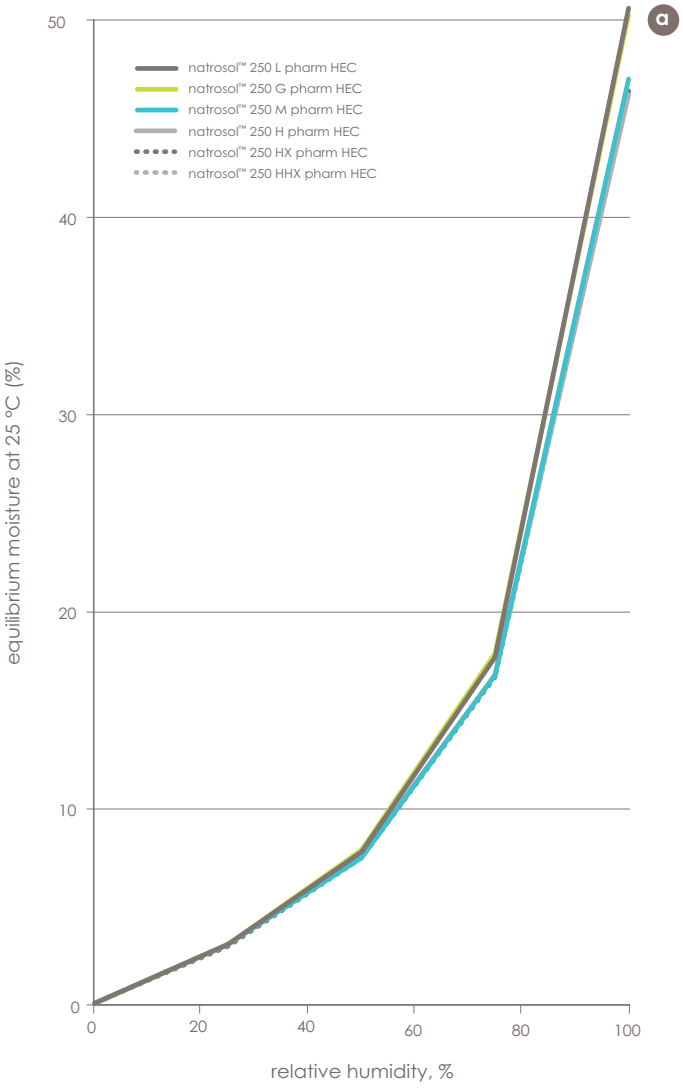
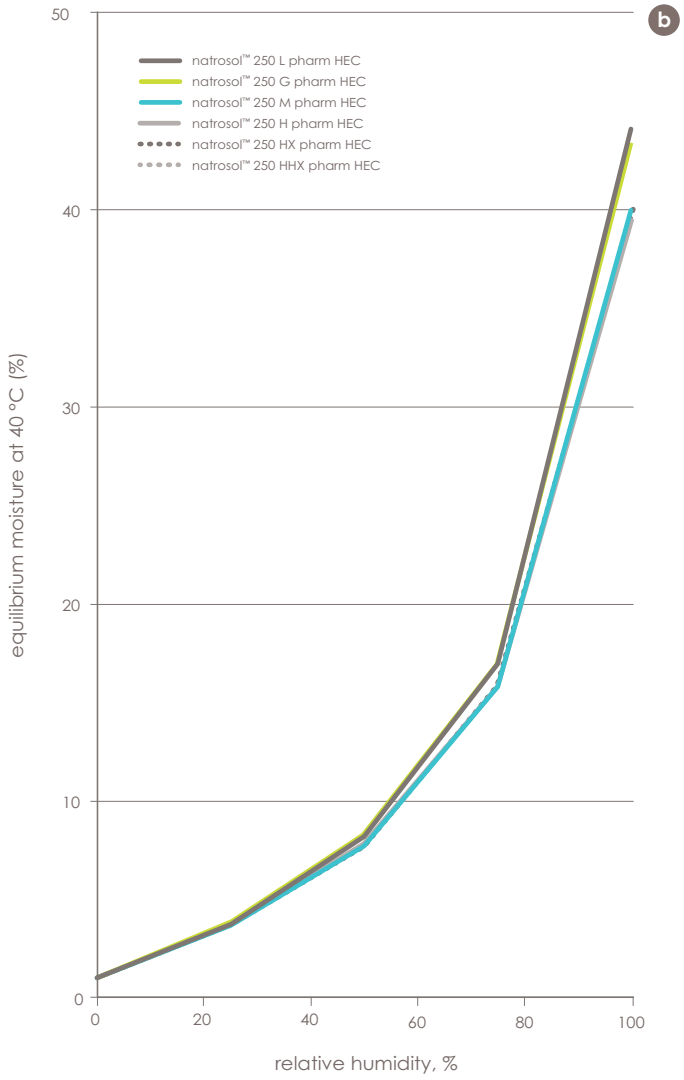


figure 3b: Equilibrium moisture content of different grades of Natrosol™ HEC at 40°C. The bold lines indicate sorption and dotted lines indicate desorption behavior.



dissolving natrosol™ 250 pharm HEC in water

Natrosol™ 250 Pharm HEC is readily soluble in either hot or cold water. However, as with most water-soluble thickeners, the particles tend to agglomerate, or lump, when first wetted with water. Thus, the time required to achieve complete solution of Natrosol™ 250 Pharm HEC is usually governed by the degree of lumping that can develop during the solution process. In general, the low-viscosity grades are more easily dissolved than the high-viscosity grades. Employing these methods will facilitate the quick preparation of solutions of Natrosol™ 250 Pharm HEC:

method 1: stirring

Natrosol™ 250 Pharm HEC is sifted slowly into the vortex of vigorously agitated water. The rate of addition should be slow enough for the particles to separate without lump formation, but not so slow that the solution thickens appreciably before all the solids are added. Agitation should be continued until all the swollen or gelatinized particles are dissolved to yield a smooth solution.

method 2: use of water miscible organic solvent

Excellent solution rates can be obtained by prewetting Natrosol™ 250 Pharm HEC with a water-miscible organic liquid before the powder is added to water. Anhydrous ethyl alcohol is suitable for this use, as are other organic liquids such as propylene glycol and glycerin.

method 3: blending with other water insoluble materials

Improved solution rates can be obtained by dry-blending Natrosol™ 250 Pharm HEC with other dry components (preferably water insoluble) contained in the formulation prior to dispersing in water. This technique effectively separates particles of Natrosol™ 250 Pharm HEC so that no lumping is experienced when the dry mix is added to water.

microbial limits

Natrosol™ 250 Pharm HEC grades are routinely sampled and subjected to microbiological testing by an independent laboratory to ensure compliance with good manufacturing practices. This testing is not done on a lot-by-lot basis, and Ashland does not make microbiological specifications for this product. Although the data generated are not intended to provide product specifications, typical results obtained using our standard protocols are as shown.

aerobic plate count, cfu/g	<100
mold, cfu/g	<100
yeast, cfu/g	<100
coliforms, MPN/g	<30
Escherichia coli/10 g	negative
Staphylococcus aureus/10 g	negative
Salmonella spp./25 g	negative
Pseudomonas aeruginosa/10 g	negative

Ashland uses officially approved methods to test products but recommends that users of Natrosol 250 Pharm HEC assure themselves of compliance with any microbiological specification that the user may have by testing each lot.

properties of solutions and gels of natrosol™ 250 pharm HEC

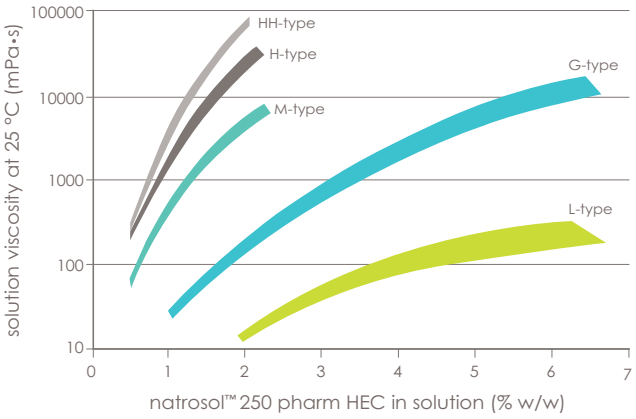
viscosity

All polymer solutions and many pharmaceutical formulations such as syrups, dispersions, emulsions, gels and creams are examples of non-Newtonian fluids. This means that their viscosities are not fixed, but rather are dependent upon the degree of shear to which they are exposed. By far the most common form of non-Newtonian behavior is shear-thinning or pseudoplastic flow, where the viscosity decreases with increasing shear rate. Solutions of Natrosol™ 250 Pharm HEC are examples of shear-thinning materials. Thus, if a solution of high-viscosity Natrosol™ 250 Pharm HEC appears to be a viscous liquid as it is poured from a bottle, it can behave as a runny liquid when applied as a lotion to the skin, and yet when high stress is removed, it will quickly revert to its original high viscosity. Because of this behavior, Natrosol™ 250 Pharm HEC is extensively used to modify the viscosity of solutions, dispersions, and emulsions. Depending on the selected grade and the concentration used, a wide variety of viscosities can be achieved with Natrosol™ 250 Pharm HEC. Thus, solution viscosity is dependent on several factors, which will be discussed in detail.

effect of concentration

When Natrosol™ 250 Pharm HEC is dissolved in water, the viscosity of the aqueous solution increases with increasing concentration and molecular weight, as shown in figure 4.

figure 4: Effect of concentration on viscosity of aqueous solutions of Natrosol™ 250 Pharm HEC.



Any desired thickening efficiency can be achieved with the wide variety of Natrosol™ 250 Pharm HEC grades available.

effect of shear rate

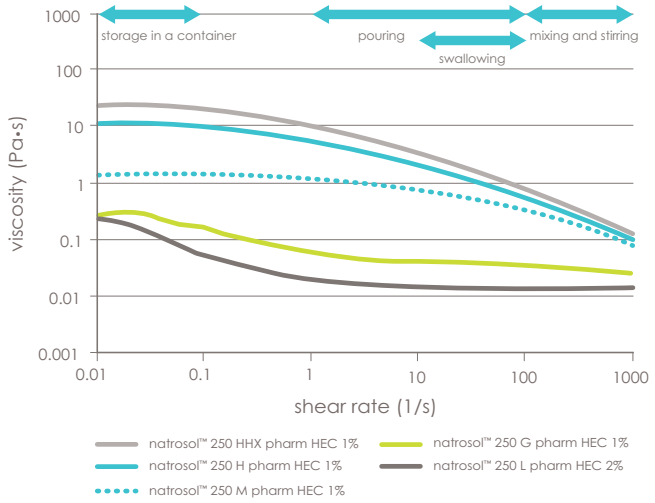
A formulation encounters different levels and kinds of shear during production, packaging, storing over its shelf life and during application. These shear forces differ depending upon the type of formulation, container-closure system and the type of application.

Shear thinning properties of Natrosol™ 250 Pharm HEC solutions can contribute different required attributes to a product, such as formulation stability or ease of application/pouring when a stress is applied. Understanding the impact of these shear forces on solution rheology provides formulators with perspective on formulation development to maintain functionality and stability under varying shear forces.

For non-Newtonian products, measuring viscosity at a single shear rate does not provide the full picture. A flow curve of viscosity across a range of shear rates, from which a viscosity value at a shear rate relevant to the process or product use conditions can be determined, is far more meaningful.

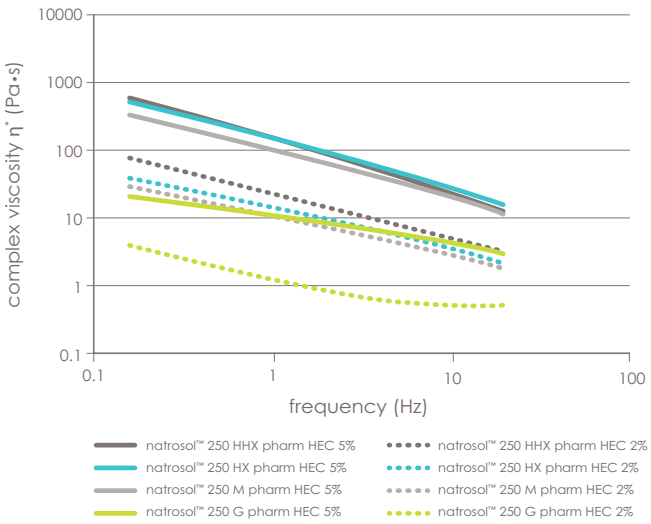
As shown in figure 5, most tested grades of Natrosol™ 250 Pharm HEC will behave similarly in terms of flow behavior, but to varying degrees, and eventually, the lower the molecular weight, the lower the change in viscosity that occurs under varied stress conditions (as shown in the typical ranges at the top of figure 5).

figure 5: Effect of shear rate on viscosity for solutions containing different grades of Natrosol™ 250 Pharm HEC grades.



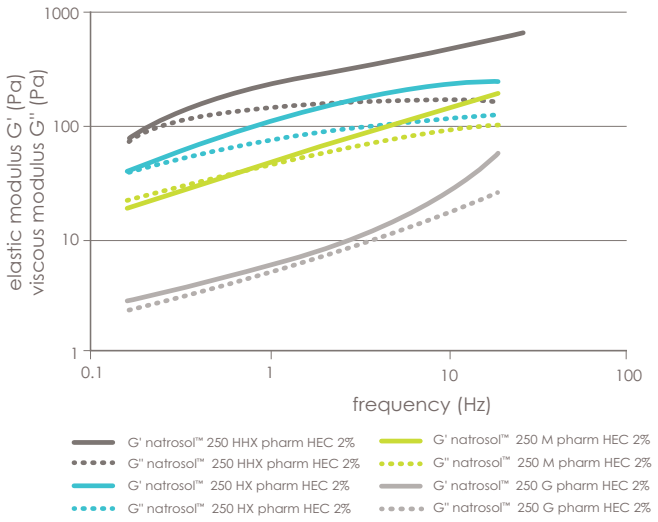
By increasing the concentration of Natrosol™ 250 Pharm HEC in water, the dissolved polymer particles form a three-dimensional network, which produces solid-like properties. These polymer gels possess both elastic (solid-like) and viscous (liquid-like) properties, which means they are viscoelastic. The data shown in figure 6 illustrate the viscoelastic properties of aqueous gels containing Natrosol™ 250 Pharm HEC at different concentrations and molecular weights, measured in an oscillating disc rheometer at increasing frequencies. Typically, the complex viscosity of HEC gels is high at low frequencies and decreases monotonically as the frequency is increased, which is a characteristic of viscoelastic systems.

figure 6: Eeffect of polymer grade, concentration, and oscillatory frequency on the viscosity of Natrosol™ 250 Pharm HEC gels.



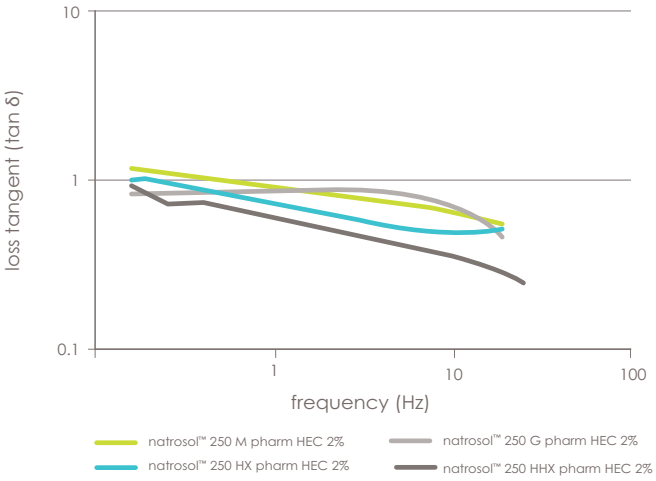
Spreadability of pharmaceutical gels and other semisolids is the result of a combination of rheological behaviors, of which viscosity is just one. In addition, structural and viscoelastic characteristics that describe the rigidity, strength and relative contributions of the elastic and viscous behaviors of a material play important roles in spreadability. The usual way to quantify viscoelastic properties is to measure the elastic or storage modulus (G') and viscous or loss modulus (G'') of the material. The storage modulus is proportional to the extent of elastic component (the solid-like component, contributed by crosslinking, entanglement, and/or aggregation) of the system, while the loss modulus is proportional to the extent of viscous component (contributed by the liquid-like portion) of the system. Gels (and creams) cannot relax quickly and are highly elastic at similar frequency ranges, and thus, the elastic modulus (G') tends to be considerably higher than the viscous modulus (G''), as shown in figure 7.

figure 7: Effect of polymer grade and oscillatory frequency on viscoelastic properties of gels containing Natrosol™ 250 Pharm HEC.



The ratio of viscous modulus (G'') to elastic modulus (G') is commonly employed to characterize the relationship between these two parameters. This parameter is called the loss tangent (tan δ), a dimensionless parameter that provides a comparative measure of both the elastic and viscous contributions (figure 8). While both loss and storage moduli increased as a function of frequency, the decrease in tan δ indicates greater elastic character of the aqueous polymeric gels. The smaller the tan δ, the more rubbery or elastomeric is the behavior.

figure 8: The effects of polymer grade and oscillatory frequency on the loss tangent (tan δ) of gels containing Natrosol™ 250 Pharm HEC.



Natrosol™ 250 Pharm HEC shows a decreasing loss tangent with increasing frequency, which translates to excellent skin feel.

effect of temperature

The viscosities of aqueous solutions of Natrosol™ 250 Pharm HEC change with temperature, increasing when cooled and decreasing when heated. The effect of temperature on the viscosity of solutions of Natrosol™ 250 Pharm HX HEC at 1% in aqueous solution is shown for example in figure 9. The effect on viscosity is the only influence temperature has on solutions of Natrosol™ 250 Pharm HEC. In contrast to some other cellulose ethers, like methylcellulose, hydroxypropylmethylcellulose or hydroxypropylcellulose, Natrosol™ 250 Pharm HEC does not exhibit a cloud point (or gelation point), and solutions of HEC may be boiled without precipitation or gelling issues.

figure 9: Effect of temperature on natrosol™ 250 HX HEC.

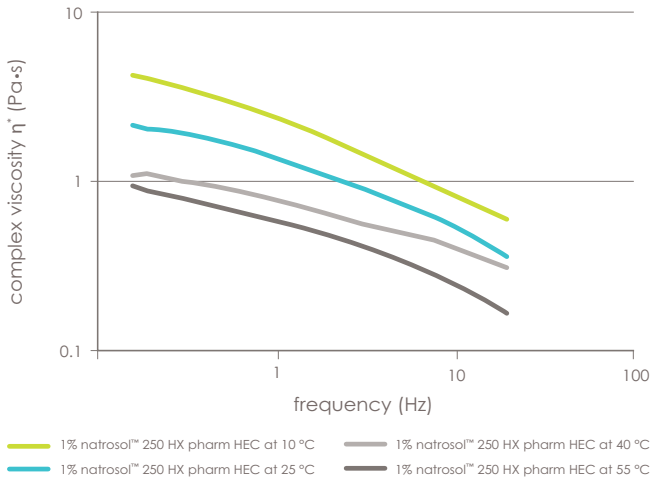
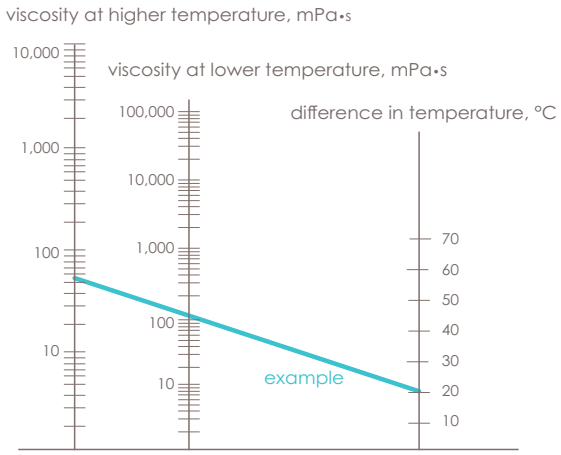


figure 10 presents a convenient nomograph that helps in estimating the viscosity of a solution of Natrosol™ 250 Pharm HEC at different temperatures starting from a known viscosity at a known temperature.

For example, the viscosity of a solution is 100 mPa·s (shown on the center line in figure 10) at 25 °C. The unknown is the viscosity when the temperature is raised by 20 °C (shown on the right line in figure 10). By placing a straightedge at 20 °C on the right line and at 100 on the center line, one can read the answer in the left column, 52 mPa·s.

figure 10: Nomograph for estimating the viscosity of solutions of Natrosol™ 250 Pharm HEC at varying temperatures.



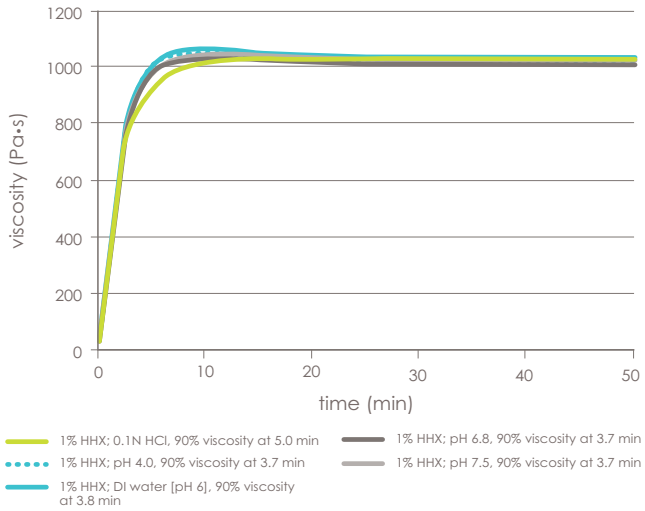
Natrosol™ 250 Pharm HEC does not exhibit a cloud point (gelation point) and viscosity of solutions change reversibly with temperature.

effect of pH

The pH of a solution of Natrosol™ 250 Pharm HEC is important for two reasons; first, because of the effect on hydrolytic breakdown, and second, because of the possible effect of pH on solution viscosity. Aqueous solutions of Natrosol™ 250 Pharm HEC are relatively stable at pH 2 to 12, with the viscosity of the solutions being largely unaffected. However, solutions possess the greatest viscosity stability in the pH range of 6.5 to 8.0. Below pH 3, solutions are less stable and may show some reduction in viscosity owing to acid hydrolysis. This behavior is common with all water-soluble polysaccharide polymers, and is accelerated by high temperature and high acidity. At high pH (highly alkaline conditions), some oxidative degradation may occur, accelerated by heat and light, that will lower the viscosity.

figure 11 illustrates polymer hydration and viscosity development of aqueous 1% Natrosol™ 250 HHX Pharm HEC solutions at different pH values. Polymer hydration and viscosity development are not affected by changes in pH.

figure 11: Polymer hydration/viscosity development of 1% Natrosol™ 250 Pharm HHX HEC solution. Hydration time was taken as the time in minutes to achieve 90% of the final viscosity, where the final viscosity was taken as the average of the last 10 minutes' viscosity during a 50 minute trial.



Solutions of Natrosol™ 250 Pharm HEC are stable over a broad pH range, with the viscosity of the solutions being largely unaffected.

mechanical properties of natrosol™ 250 pharm HEC gels

Textural properties should be considered in the design of topical formulations, e.g., ease of removal from the tube, ease of application on skin, retention of the product at the site of application and the feel of the product after application. One method to measure the mechanical and adhesive properties of pharmaceutical gels containing Natrosol™ 250 Pharm HEC is texture profile analysis. Typical results from this kind of test are presented in table 5.

The grades evaluated in table 5 show a wide range of mechanical and adhesive properties that are significantly (and sequentially) affected by changes in the weight average molecular weight and polymer concentration. Increasing firmness indicates a stronger gel due to higher resistance to deformation, and, eventually, the gel network would be more rigid with increasing molecular weight and/or concentration. Work of shear is a measurement of consistency and the inverse of spreadability. Higher values indicate a thicker consistency. The more negative the value for stickiness, the more sticky or cohesive is the sample. Topical preparations should exhibit mechanical characteristics such as ease of removal from the product container, as well as good spreadability on and adhesion to the skin; however, a compromise must be made between product adhesiveness (stickiness on the skin), firmness (ease of removal from container) and spreadability (ease of application on the skin).

table 5: Mechanical properties of Natrosol™ 250 Pharm HEC gels as determined using texture profile analysis (n=3, average ± standard deviation).

grade	weight average molecular weight (da)	conc. % (w/v)	firmness/hardness (g)	work of shear (g·s)	stickiness (g)
G	300,000	2	15.53	7.55	−19.6
		3.5	68 ± 2	30 ± 5	−91 ± 3
		5	261 ± 4	120 ± 7	−349 ± 3
M	720,000	2	168 ± 8.67	86 ± 15.77	−145 ± 8
		3.5	638 ± 16	423 ± 18	−523 ± 12
		5	1761 ± 23	1374 ± 27	−1437 ± 35
HX	1,000,000	2	258 ± 6	155 ± 18	−199 ± 9
		3.5	1049 ± 13	865 ± 7	−775 ± 14
		5	2315 ± 113	2101 ± 123	−1676 ± 87
HHX	1,300,000	2	433 ± 25	315 ± 23	−323 ± 17
		3.5	1371 ± 94	1132 ± 148	−964 ± 53
		5	3168 ± 17	2918 ± 163	−2145 ± 22

Mechanical properties of pharmaceutical gels (such as hardness, stickiness and spreadability) can be set precisely by varying grade and concentration of Natrosol™ 250 Pharm HEC.

antimicrobial preservatives

Aqueous solutions of Natrosol™ 250 Pharm HEC are subject to enzymatic degradation, with consequent loss in solution viscosity. Enzymes that catalyze this degradation are produced by many bacteria and fungi present in the environment. Therefore, it is recommended that an antimicrobial preservative is added when aqueous solutions are to be stored.

Natrosol™ 250 Pharm HEC can be used with a wide variety of water-soluble antimicrobial preservatives, however it may decrease the antimicrobial activity of various preservatives. Care should be taken in finding an effective preservative concentration while ensuring that the concentration remains below an irritating/ toxic concentration.

heat sterilization and sterile filtration

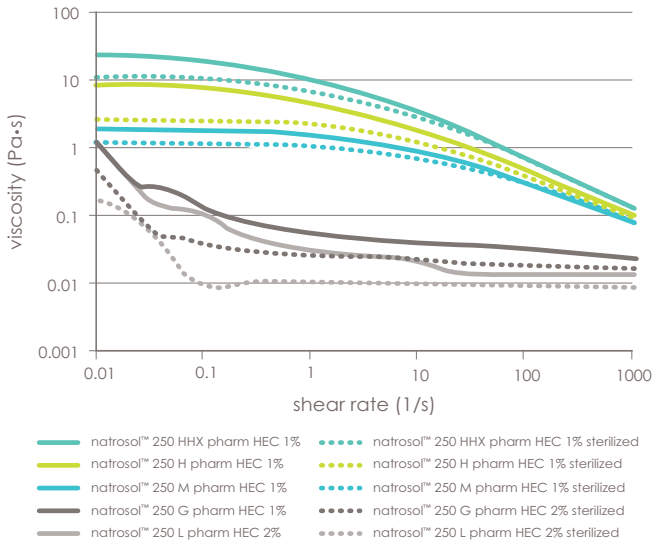
As an alternative to adding antimicrobial preservatives, some consideration might also be given to sterile filtration or heat sterilization.

heat sterilization

Heat sterilization can alter molecular weight of polymers like Natrosol™ 250 Pharm HEC. Exposure to high temperature and pressure may lead to breakdown of long polymer chains, often leading to a drop in viscosity. The drop in viscosity does not occur to the same extent for all molecular weight grades, and thus, optimization of a formulation is necessary to make sure that any viscosity drop is taken into account in the final formulation. The data shown in figure 12 illustrate the rheological behavior changes in solutions made with various Natrosol™ 250 Pharm HEC grades at different concentrations after moist heat sterilization (autoclave: 121 °C; 20 min).

Based on these data, a substantial decrease in viscosity can be observed after sterilization. Therefore, the grade of Natrosol™ 250 Pharm HEC should be carefully selected when moist heat sterilization will be applied to the product.

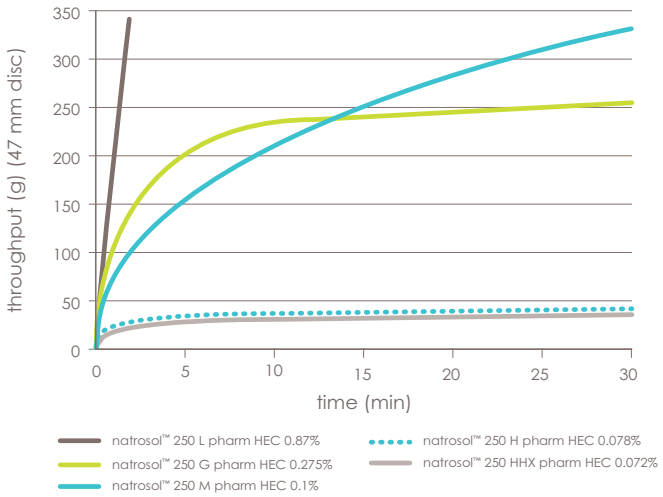
figure 12: Effect of moist heat sterilization on rheological properties of solutions of various Natrosol™ 250 Pharm HEC grades.



sterile filtration

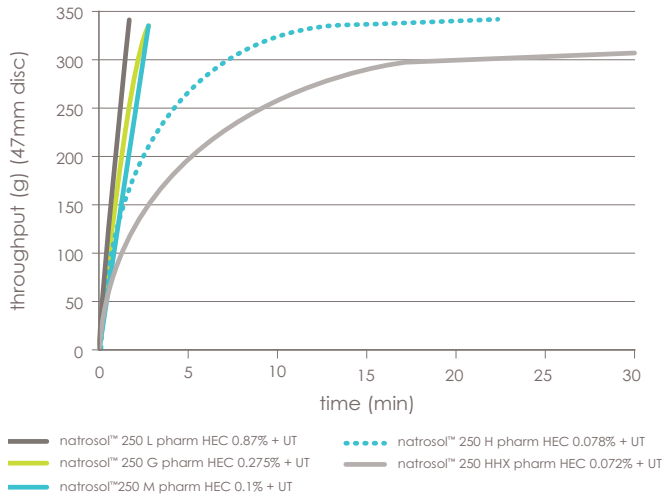
Sterilizing filtration is the process of removing microorganisms from a fluid stream without adversely affecting the product by heat or radiation. It is an aseptic process, typically using 0.2 µm-rated sterilizing grade filters, that is commonly employed in the preparation of biopharmaceuticals. Solutions containing viscosity enhancers like Natrosol™ 250 Pharm HEC can occasionally cause difficulties during sterile filtration, such as filter blockage. This would result in frequent filter changeouts, increased processing time, and product loss. The data shown in figure 13 illustrate the filterability of solutions of various grades of Natrosol™ 250 Pharm HEC tested at different concentrations to achieve a viscosity of 5 mPa·s. A steeper curve shows superior filterability. Filter material for sterile filtration was Supor® EX grade ECV sterilizing grade filter (asymmetric polyethersulfone [PES] / symmetric PES; Pall Life Sciences, Basel, CH) with 47 mm diameter.

figure 13: Filterability of various grades of Natrosol™ 250 Pharm HEC at an adjusted viscosity of 5 mPa·s.



By applying a short period of high shear forces to the system, the filterability of all Natrosol™ 250 Pharm HEC grades can be significantly improved. This period of high shear mixing does not significantly impact the viscosity and/or molecular weight of the solutions. By using this method of preparation, all Natrosol™ 250 Pharm HEC grades become viable options for preparation of products via sterile filtration.

figure 14: Filterability of various grades of Natrosol™ 250 Pharm HEC at an adjusted viscosity of 5 mPa·s using an additional 2 min of 20000 RPM rotor stator stirring.



Natrosol™ 250 Pharm HEC grades can be either sterilized or sterile filtered, depending on the other formulation ingredients.

synergistic effect with sodium carboxymethylcellulose

Natrosol™ 250 Pharm HEC does not exhibit thixotropic behavior, per se. Therefore, it is seldom used for pharmaceutical suspensions alone. However, when a solution of non-ionic Natrosol™ 250 Pharm HEC is blended with a solution of anionic sodium carboxymethylcellulose (Blanose™ or Aqualon™ CMC), a synergistic effect on viscosity is typically observed. CMC has been widely used in pharmaceutical suspensions and shows varying degrees of thixotropy. Such a polymer mixture produces solution viscosities considerably higher than would ordinarily be expected given the solution viscosities of both polymers alone, and furthermore, this combination makes it possible to incorporate thixotropic behavior into formulations containing HEC as a suspending agent, which would not otherwise be entirely suitable for pharmaceutical suspensions. table 6 shows combinations of both polymers, the resulting viscosities at a shear rate of 10^{5-1} of the mixtures, and the resulting viscosities of the pure polymer grades at 1% use level, indicating the viscosity without the synergistic effect.

table 6: Synergistic effect on viscosity of Natrosol™ 250 Pharm HEC with Blanose™ CMC.

polymers used	concentration	viscosity at 10 s^{-1} (mPa·s)
natrosol™ 250H HEC	1%	1780
blanose™ 7H3SF CMC	1%	1490
natrosol™ 250H HEC + blanose™ 7H3SF CMC	0.5% each	2370
natrosol™250M HEC	1%	850
blanose™ 7H3SF CMC	1%	1490
natrosol™ 250M HEC + blanose™ 7H3SF CMC	0.5% each	1850
natrosol™ 250M HEC	1%	850
blanose™ 7H4XF CMC	1%	2740
natrosol™250M HEC + blanose™ 7H4XF CMC	0.5% each	2530
natrosol™ 250M HEC	1%	850
blanose™ 7HF CMC	1%	1750
natrosol™ 250M HEC + blanose™ 7HF CMC	0.5% each	1870
natrosol™ 250M HEC	1%	850
blanose™ 7M31F CMC	1%	220
natrosol™ 250M HEC + blanose™ 7M31F CMC	0.5% each	720

The combination of Natrosol™ 250 Pharm HEC and Blanose™ CMC provides a synergistic effect on viscosity and incorporates thixotropic behavior into the formulation.

tolerance for inorganic salts

Because of its solubility and nonionic character, Natrosol™ 250 Pharm HEC has good tolerance for dissolved electrolytes, although it may precipitate when mixed with high-salinity solutions. Data in table 7 show that Natrosol™ 250 Pharm HEC is soluble in most 10% salt solutions, excluding disodium phosphate and sodium sulfate, and some of the 50% (saturated) salt solutions. In obtaining these data, 1 ml of a solution of Natrosol™ 250 Pharm HEC was added to 15 g of each of the salt solutions. The ratio of Natrosol™ 250 Pharm HEC to salt solids ranged from 1:150 to 1:750.

table 7: compatibility of solutions of natrosol™ 250

salt	10% salt Solution	50% salt (saturated)
sodium tetraborate	C	C
calcium chloride	C	C
calcium sulfate	C	C
disodium phosphate	P	P
ferric sulfate	C	C
magnesium chloride	C	C
magnesium sulfate	C	P
sodium acetate	C	C
sodium chloride	C	C
sodium sulfate	P	P
trisodium phosphate	C	P
zinc sulfate	C	P

(C – compatible, P – precipitates)

compatibility with other materials

The nonionic nature of Natrosol™ 250 Pharm HEC makes it compatible with a broad range of water-soluble materials, including other water-soluble polymers and natural gums.

Table 8 lists the viscosity and appearance of solutions of Natrosol™ 250 Pharm HEC and some common additives in pharmaceutical formulations. The data were obtained by adding a medium viscosity Natrosol™ 250 M Pharm HEC grade to the respective additive (solution), with moderate stirring to ensure that the Natrosol™ 250 Pharm HEC was completely dissolved.

Natrosol™ 250 Pharm HEC is compatible in solutions with many inorganic salts, as well as with a broad range of other materials such as surfactants, solubilizers, and preservatives.

table 8: Effect of formulation additives on properties of solutions of Natrosol™ 250 M Pharm HEC and water.

material	additive %	HEC %	viscosity after 48 hours (mPa·s)	appearance after 48 hours
polymers				
klucel™ HF HPC	1	1	22000	hazy
klucel HF HPC	0.5	1	13000	hazy
guar gum	0.5	1	7900	opaque
xanthan gum	0.5	1	6700	opaque
surfactants				
sodium lauryl sulfate	1	1	580	clear
tween 60	1	1	1850	slightly hazy
tween 80	1	1	2500	clear
cetyl trimethylammonium bromide	1	1	1520	clear
triethanolamine	1	1	2950	clear
preservatives				
sodium benzoate	0.5	1	2500	clear
methyl paraben	0.2	1	2100	clear

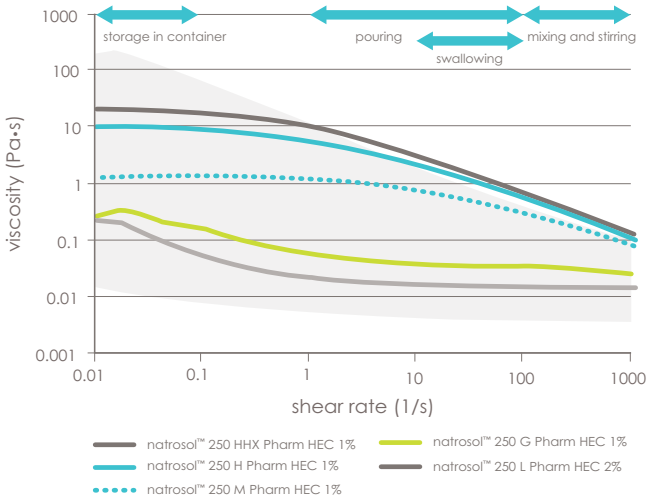
application examples for natrosol™ 250 pharm HEC

natrosol™ 250 pharm HEC as a viscosity modifier in pharmaceutical oral liquids

Oral solutions are liquid preparations in which the active pharmaceutical ingredient (API) and other excipients are dissolved in a suitable solvent system, consisting mainly of water. Because the API is dissolved in the formulation, it is usually immediately available for absorption. Oral solutions containing high concentrations of sucrose or other sugars traditionally have been defined as syrups. There is an increasing trend to replace sucrose in whole or in part with other substances because of its glycogenic and cariogenic properties. Cellulose ethers (e.g., Natrosol™ hydroxyethylcellulose) are non-glycogenic, because they are not hydrolyzed and absorbed into the blood stream. Subsequently, when dissolved, they form a syrup-like vehicle for medications intended for use by diabetic patients and others whose diet must be restricted to non-glycogenic substances. The viscosity resulting from the use of these cellulose derivatives is much like that of a sucrose syrup. The addition of one or more artificial sweeteners usually produces an excellent imitation of a traditional syrup.

The shaded portion of figure 15 represents the viscosity ranges of 23 tested commercial syrup products. The shear stress profiles indicate that different grades of Natrosol™ 250 Pharm HEC with varying concentrations are positioned across the entire range of rheological profiles of analyzed, marketed syrup formulations.

figure 15: Effect of shear on viscosity for various Natrosol™ 250 Pharm HEC grades in relation to commercial syrups (gray area).



Tested grades of Natrosol™ 250 Pharm HEC are suitable to match typical viscosity profiles of pharmaceutical syrups.

The following case studies exemplify the use of the different grades of Natrosol™ 250 Pharm HEC for development of sugarless syrup formulations.

case study: sugar-free ambroxol syrup

Ambroxol stimulates mucus secretion and promotes a normalization of mucus viscosity for treatment of respiratory diseases. Formulation details are described in table 9. As seen in figure 16, all formulations are clear.

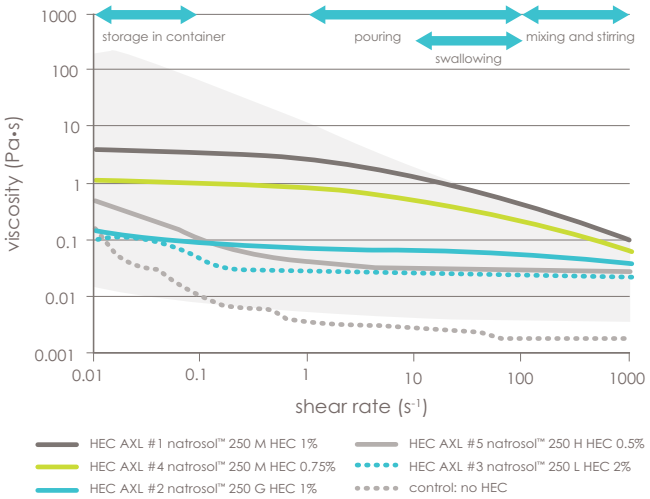
table 9: Formulation of ambroxol syrups using various Natrosol™ 250 Pharm HEC grades.

ingredient	content (%)	functional use
ambroxol HCl	0.6	active pharmaceutical ingredient
benzoic acid	0.2	preservative
propylene glycol	10	solvent
sorbitol 70%	5	sweetener
sucralose	0.5	sweetener
apricot flavor	0.1	flavor
natrosol™ 250 HEC	0.0–2.0	viscosity modifier
water, demineralized	q.s. to 100	aqueous vehicle

figure 16: Photographs of ambroxol formulations using varying amounts of different Natrosol™ 250 Pharm HEC grades.

The rheological profiles shown in figure 17 indicate that Natrosol™ 250 Pharm HEC helps the formulation achieve the desired rheological profile, which can't be achieved without the use of a viscosity modifier. The formulation without a viscosity modifier does not show the necessary behavior for most of the operations exhibiting varying degrees of shear on the formulation. Its viscosity is comparable low at higher shear rates, almost water like, making pouring the syrup onto a spoon challenging. The desired viscosity can be adjusted by choosing the appropriate grade and concentration of Natrosol™ HEC.

figure 17: Effect of shear on viscosity for various Natrosol™ 250 Pharm HEC grades used for an ambroxol syrup at different concentrations.



case study:
taste-masked loratadine syrup

Loratadine is used to alleviate allergy symptoms. Formulation details are described in table 10. As can be seen in figure 18, all formulations are clear.

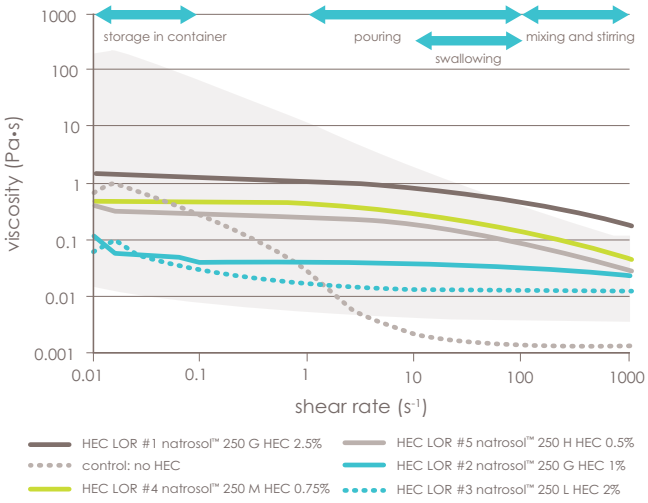
table 10: Formulation of loratadine syrups using various Natrosol™ 250 Pharm HEC grades.

ingredient	content (%)	functional Use
loratadine	0.1	active pharmaceutical ingredient
ethanol 96%	2.5	solvent for api in preparation (later mostly evaporated)
citric acid	0.05	solubilizer for api
CAVASOL® W7 HP pharma 2HP-β-Cyclodextrin	2.4	solubilizer and taste masking
sorbic acid	0.1	preservative
natrosol™ 250 pharm HEC	0.0–2.0	viscosity modifier
water, demineralized	q.s. to 100	aqueous vehicle

figure 18: Photographs of loratadine formulations using varying amounts of different Natrosol™ 250 Pharm HEC grades.

The same basic conclusions as those obtained for the sugar-free ambroxol syrup can be drawn here. The inconsistent shape of the curve without viscosifier, seen in figure 19, stems from the use of 2-hydroxypropyl β-cyclodextrin in the formulation. This inconsistent rheological profile is controlled once a viscosifier is introduced to the formulation. The desired viscosity can be adjusted by choosing the right grade and concentration.

figure 19: Effect of shear on viscosity for various Natrosol™ 250 Pharm HEC grades used for a loratadine syrup at different concentrations.



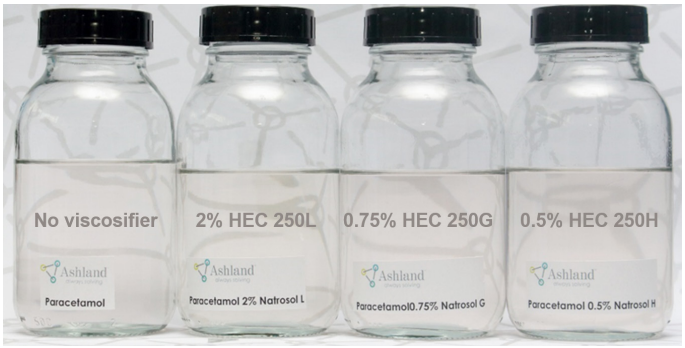
case study:
syrup for poorly soluble paracetamol

Paracetamol is widely used as an analgesic and antipyretic drug. It is well absorbed in the gastrointestinal tract, showing a dose-dependent oral bioavailability. Formulation details are described in table 11. As can be seen in figure 20, all formulations are clear.

table 11: Formulation of paracetamol syrups using various Natrosol™ 250 Pharm HEC grades

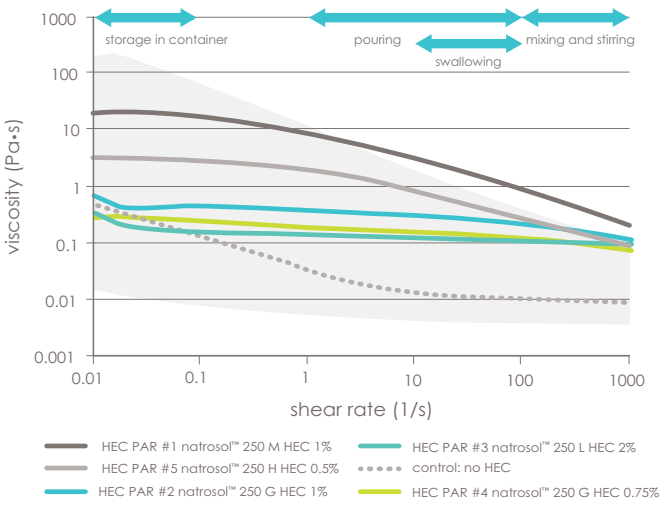
ingredient	content (%)	functional use
paracetamol	5	active pharmaceutical ingredient
sodium benzoate	0.1	preservative
propylene glycol	45	solvent
sorbitol 70%	5	sweetener
sucralose	0.5	sweetener
apricot flavor	0.1	flavor
natrosol™ 250 pharm HEC	0.0–2.0	viscosity modifier
water, demineralized	q.s. to 100	aqueous vehicle

figure 20: Photographs of paracetamol formulations using varying amounts of different Natrosol™ 250 Pharm HEC grades.



The rheological profiles obtained (see figure 21) indicate that Natrosol™ 250 Pharm HEC effectively enables the desired rheological behavior to be achieved. While the formulation without a viscosity modifier produces a rheological profile within the range of investigated commercial syrup formulations, it does show a drop in viscosity at shear rates equivalent to pouring the formulation out of its bottle, which is undesirable in a syrup formulation. This effect is not observed for the formulations containing Natrosol™ 250 Pharm HEC, and the desired viscosity can be adjusted by choosing the right grade and concentration.

figure 21: Effect of shear on viscosity for various Natrosol™ 250 Pharm HEC grades used for a paracetamol syrup at different concentrations.

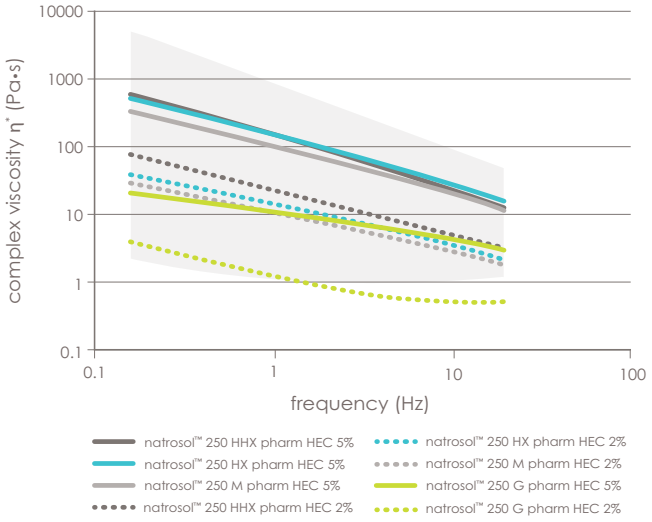


natrosol™ 250 pharm HEC as rheology modifier and structured vehicle promoter for semi-solid formulations

Gel-forming hydrophilic polymers are typically used to prepare lipid-free semisolid dosage forms, including dental, topical, nasal, ophthalmic, rectal and vaginal gels. In the development of topical dosage forms, several desirable attributes contribute to patient acceptability and clinical efficacy. These attributes include mechanical and rheological properties (e.g., viscosity, ease of removal of product from the container, good spreadability on the skin, good adhesion to ensure retention), as well as the influence of the gel former on drug release and drug absorption.

Products designed for topical administration will be subjected to various shearing forces that occur on removal of the product from its container, application to the skin, and during flexing of the skin. figure 22 shows the complex viscosities of gels made from various grades of Natrosol™ 250 Pharm HEC, measured using oscillating rheometry. The shaded portion of figure 22 represents the viscosity range of several tested, commercial gel products. The rheological profiles indicate that different grades and concentrations of Natrosol™ 250 Pharm HEC cover a wide range of rheological behaviors and viscosities to match marketed gel formulations.

figure 22: The effects of polymer grade, concentration, and oscillatory frequency on the dynamic viscosity of Natrosol™ 250 Pharm HEC hydrogels in relation to commercial topical gels (gray area).



Higher molecular weight grades of Natrosol™ 250 Pharm HEC (G, M, HX, and HHX grades) are the preferred pharmaceutical gel formers.

case study: diclofenac gel

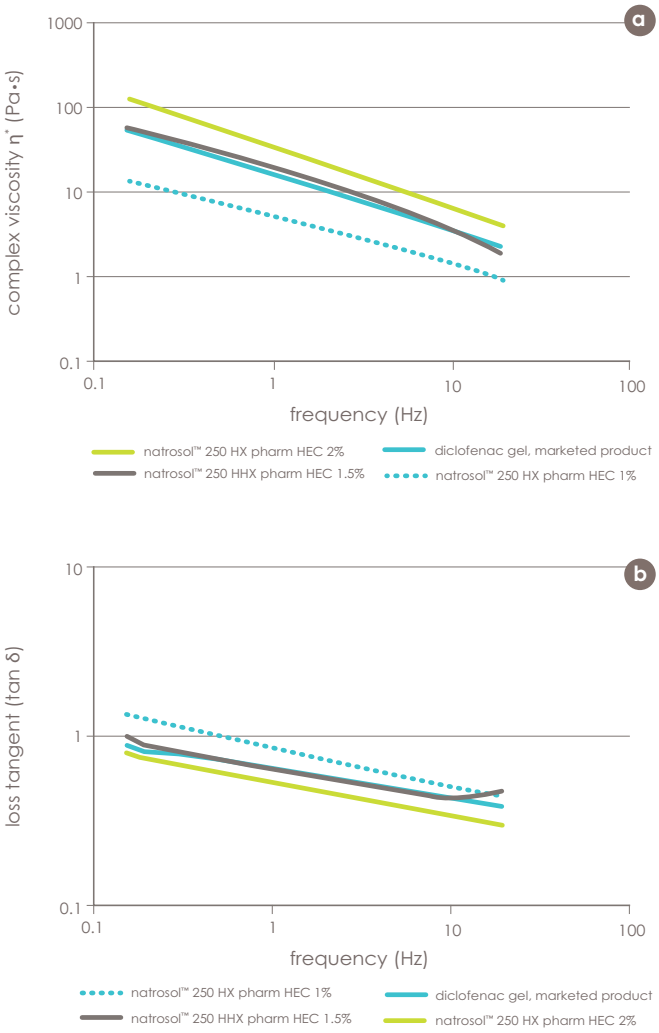
Natrosol™ 250 Pharm HEC is a non-ionic polymer and, thus, more resistant to electrolytes and salts present in topical formulations compared with ionic viscosifiers. In this case study, the highest viscosity grade, Natrosol™ 250 HHX Pharm HEC was used. However, similar results can be achieved by using other grades and concentrations of Natrosol™ 250 Pharm HEC. table 12 illustrates the composition of a typical formulation.

table 12: Formulation composition of diclofenac gel.

ingredient	content (%)	functional use
diclofenac potassium	1	active
propylene glycol	30	co-solvent/ Solubilizer
natrosol™ 250 HHX pharm HEC	1, 1.5 or 2	gelling agent
water	q.s. 100	aqueous vehicle

Formulations containing varying concentrations of Natrosol™ 250 HHX Pharm (1, 1.5, and 2%, respectively) were compared with a commercially available diclofenac gel formulation. All gels were characterized in terms of their rheological, mechanical and textural properties. This information can be used to select a suitable candidate formulation and to predict the effects of physiological stresses on product performance. The rheological behavior of the gels is strictly related to polymer concentration. The elasticity of the gels increased with increasing concentration from 1% to 2%, as illustrated by the decreasing values of tan δ. Viscosity decreased with increasing frequency, showing a shear thinning behavior. Results from the rheological profiling also reveal that the viscoelastic properties of a formulation containing 1.5% Natrosol™ 250 HHX Pharm HEC were very close to the viscoelastic properties of the marketed product (figure 23).

figure 23: Viscosity (a) and tan δ (b) of diclofenac formulations.



As described in table 13, the concentration of Natrosol™ 250 Pharm HEC also has a significant effect on the mechanical properties of the gels. With increasing concentrations of Natrosol™ 250 Pharm HEC, the gels showed a greater resistance to deformation, as the values for hardness increased. Furthermore, a higher concentration of Natrosol™ 250 Pharm HEC results in a thicker consistency, as shown by an increase in the work of shear. Finally, the stickiness of the gels is also directly related to the concentration, more 'sticky' or 'cohesive' gels were obtained at higher concentrations of Natrosol™.

table 13: Mechanical properties of gels containing diclofenac as determined using texture profile analysis (n=3, average ± standard deviation).

formulation	firmness/ hardness (g)	work of shear (g·s)	stickiness (g)
diclofenac gel, commercial reference	203 ± 3	152 ± 8	−142 ± 2
formulation 1 containing 1% natrosol™ 250 HHX	107 ± 17	81 ± 1	−84 ± 1
formulation 2 containing 1.5% natrosol™ 250 HHX	286 ± 6	239 ± 67	−208 ± 69
formulation 3 containing 2% natrosol™ 250 HHX	487 ± 4	444 ± 21	−346 ± 1

case study: aluminum hydroxide oral gel

Aluminum hydroxide ($Al[OH]_3$) is an antacid commonly used to relieve symptoms of heartburn, stomach upset, acid indigestion and sour stomach. Because liquid antacids tend to work faster than tablets or capsules, Natrosol™ 250 Pharm HEC was used to suspend and stabilize aluminum hydroxide in an oral gel formulation. A marketed product containing aluminum hydroxide in a gel formulation served as a benchmark. table 14 illustrates the composition of such an oral gel. The equivalent amount of aluminum hydroxide per single dose is 320 mg per 5 ml.

table 14: Formulation of aluminum hydroxide oral gel.

ingredient	content (%)	functional use
aluminum hydroxide (70% assay)	9.14	active
glycerin	4	humectant
sorbitol	7	sweetening agent
polysorbate 80	1	surfactant
simethicone	0.1	anti-foaming agent
natrosol™ 250 M pharm HEC	0.5/0.75	viscosity modifier
water	q.s. to 100	aqueous vehicle

The oral gel antacid suspensions were evaluated for composition and product quality. Natrosol™ 250 M Pharm HEC served as viscosity modifier to reduce settling of the suspended particles and to match the rheological properties of the marketed product. The data in figure 24 illustrate how slight changes in the content of Natrosol™ 250 M Pharm HEC result in different rheological profiles. Although it is possible to prevent settling of the particles simply by increasing the viscosity, there is a further important requirement that the suspension should be sufficiently pourable for dosing, e.g., out of the bottle into a measuring cup or spoon. Nevertheless, the use of Natrosol™ 250 M Pharm HEC to increase viscosity is an important part of formulation development, and allows for adjusting the rheological properties of the formulation to prepare either a more gel-like or a more liquid-like formulation.

figure 24: Viscosity of aluminum hydroxide formulations

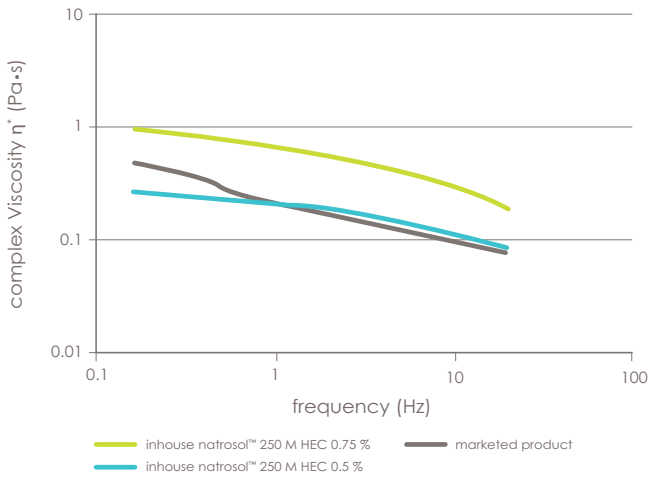
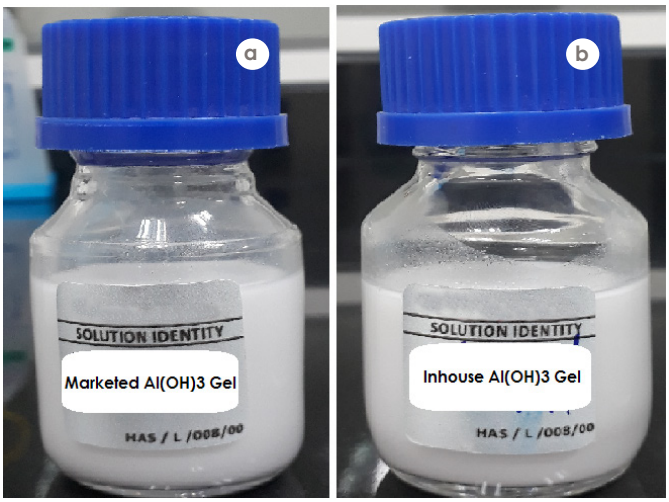


figure 25 illustrates the uniform dispersion of aluminum hydroxide both in the marketed and the HEC-containing formulation. There is a balance between particle size distribution, viscosity of the continuous phase and density differences between the dispersed phase and that of the continuous phase. High shear mixing was used to achieve a better disaggregation of the $Al(OH)_3$ particles, while the addition of Natrosol™ HEC, polysorbate 80 and sorbitol helped in stabilizing the suspension.

figure 25: Photographs of aluminum hydroxide suspensions. (a) Marketed formulation; (b) Formulation containing Natrosol™ 250 M Pharm HEC as a viscosity modifier.

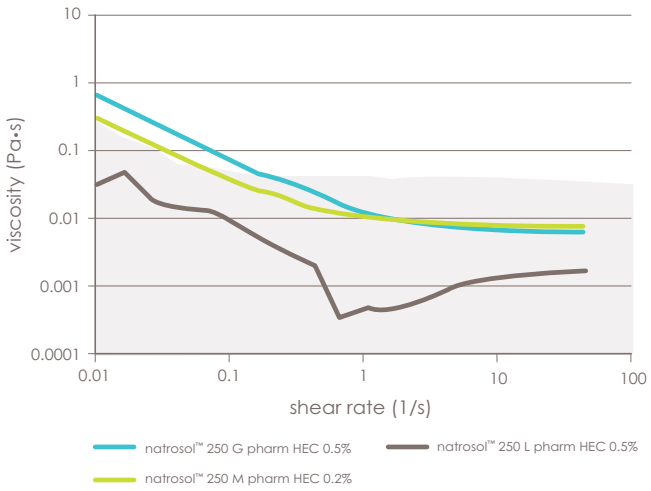


ophthalmic solutions using natrosol™ 250 pharm HEC[1]

Many marketed ophthalmic solutions are formulated with viscosifiers. Drug action from an ophthalmic solution may be prolonged by increased corneal retention or reduced drainage from the eye, when viscosity is increased. The corneal contact time of topical ophthalmic solutions typically increases with viscosity of the formulations, up to 25 mPa·s. Further increases result in reflex tearing and blinking to regain the original viscosity of lacrimal fluid (1.07 – 5.97 mPa·s), setting 25 mPa·s as the upper viscosity limit for eyedrop formulations.

The data shown in figure 26 suggest that lower molecular weight grades are the preferred choice when considering Natrosol™ 250 Pharm HEC in the development of ophthalmic solutions. The grey area marks the typical formulation range of eyedrop formulations. Depending on their concentration, low molecular weight grades of Natrosol™ 250 Pharm HEC exhibit different rheological behaviors, however, all tested grades may be used in viscous eyedrop formulations.

figure 26: Aqueous solutions of low molecular weight grades of Natrosol™ 250 Pharm HEC adjusted in their Brookfield viscosity to reflect the upper viscosity limit of 25 mPa·s.



Lower molecular weight grades of Natrosol™ 250 HEC (M, L, and G grades) are recommended as viscosifiers for ophthalmic solutions.[1]

[1]Note that Natrosol™ 250 HEC pharmaceutical grades are excipient quality and manufactured under excipient GMPs (USP <1078>; EXCiPACT). Ashland products are not sterile as supplied; further sterilization is necessary.

Based on these results, it is possible to formulate eye drops with different viscosities for longer corneal contact times. table provides model formulations for artificial tear solution. Based on the parameters tested, the different formulations exhibit different viscosities, coupled with other parameters that are close to those of human tears, such as osmolality, pH, and surface tension.

table 15: Eyedrop formulation for dry eye syndrome.

ingredient	formulation 1 (% content)	formulation 2 (% content)	functional use
natrosol™ 250 L pharm HEC	0.5	1	viscosity modifier
benzalkonium chloride	0.005	0.005	preservative
aqualon™ 7L2P CMC	0.5	1	viscosity modifier
glycerin	0.2	0.2	lubricant
EDTA	0.03	0.03	chelating agent
boric acid	3	3	buffer/antibacterial agent
sodium borate	0.04	0.04	buffer
potassium chloride	0.35	0.35	tonicity adjuster
sodium chloride	0.4	0.4	tonicity adjuster
purified water	q.s. 100%	q.s. 100%	aqueous vehicle
parameter			
pH	7.26	7.28	
osmolality (mOsmol/kg)	300	322	
viscosity (mPa·s)	4.83	15.8	
surface tension (mN/m)	38.25	38.92	

packaging and storage

Natrosol™ 250 Pharm HEC is packaged in foil-lined, multiwall 25 kg bags, stretch-wrapped, capped, and palletized for handling convenience. It is supplied from the Ashland production facilities in Zwijndrecht, the Netherlands.

Natrosol™ 250 Pharm HEC is a non-perishable powder. It is recommended to use the product in rotation on a first in, first out basis. The product should be stored under ambient conditions. The product is hygroscopic and water content of the packed product will/may increase if not stored in tightly sealed bags under dry conditions.

product safety and handling precautions

Please review our latest Safety Data Sheet (SDS) and ensure that the use you intend can be accomplished safely before using this product. Before handling any other products mentioned in the text, you should obtain available product safety information and take necessary steps to ensure safety of use.

Hydroxyethylcellulose dust may be an irritant to the eyes, and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hydroxyethylcellulose is combustible.

CAS number and name

CAS number: 9004-62-0

CAS name: cellulose, 2-hydroxyethyl ether

toxicological studies

Natrosol™ 250 Pharm HEC has found use in many pharmaceuticals and cosmetic preparations, however, Natrosol™ 250 Pharm HEC is not recommended for use in preparations for parenteral injections. Animal toxicology and human dermatology studies have been conducted on Natrosol™ 250 Pharm HEC in independent laboratories. These are available by request only and can be shared after signing a confidentiality agreement with Ashland.

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