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Review Article

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Hydroxyethylcellulose as a versatile viscosity modifier in the development of sugar-free, elegant oral liquid formulations

Vijaya Kumar J[1*], Ajay Kumar Dantuluri[1], Yi Liu[2] and Thomas Durig[3]
[1]Ashland Private Limited, India
[2]Ashland (China) Holdings Co., Ltd., China
[3]Ashland Specialty Ingredients, Wilmington, DE, USA
*Corresponding author: Vijaya Kumar J, Senior Scientist,
Ashland India Private Limited, Lab suite 23, Building 2700, 2nd Floor,
Neovantage Innovation Park Pvt Ltd., Survey No. 101, 101/2 & 340, Plot: 4,
Lalgadi Malakpet Village, Genome Valley,
Shamirpet Mandal, Hyderabad, Telangana, India 500078
Tel.: +91 40 66406512; Mob: +91 9963029283
E-mail: *vjujare@ashland.com*

Abstract

Pharmaceutical formulations in liquid form for oral administration are commonly utilized for geriatric and pediatric patients who have difficulty swallowing solid dosage forms. Rheology, texture, and stability are among the Critical Quality Attributes (CQAs) that must be addressed in the development of oral liquid dosage forms. The distribution of pharmaceutical components relies on the manipulation of rheological properties and stabilization within these forms. The utilization of thickening agents to increase the viscosity of the liquid vehicle serves to reduce particle settling. Historically, sugars such as sucrose were utilized for this purpose, as well as for masking the taste of active pharmaceutical ingredients (API). However, alternative thickening agents such as xanthan gum, tragacanth, carrageenan, and cellulose derivatives (such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose and hydroxyethylcellulose etc.) are increasingly employed as they do not possess the same risks of glycogenic and cariogenic as sugars. Cellulose derivatives, due to their water binding and viscosity modifying properties, can be effectively utilized to enhance the rheological properties and stability of oral liquid dosage forms. The use of hydroxyethylcellulose, a highly water-soluble cellulose ether polymer, as a viscosity modifying agent, as well as its underlying polymer chemistry, is thoroughly examined in this literature review.

Keywords: Cellulose Derivatives; hydroxyethylcellulose; oral Liquids; Natrosol™ 250 HEC, syrup

1. Introduction

Patients who are having trouble swallowing solid dosage forms, such as tablets and capsules, or whose required dose does not align with the available tablet or capsule strengths, as is commonly the case with pediatric and geriatric populations, may benefit from the use of oral liquid medications (Ivanovska et al., 2014; F. L. Lopez et al., 2015; Zajicek et al., 2013). The ease of measurement and administration of liquid dosage forms makes them an attractive option for these patient populations. However, the formulation and preparation of oral liquids can be complex and challenging. Additionally, oral liquids may also possess an unpleasant taste, and the use of solvents and preservatives may be restricted due to potential toxicity, particularly in pediatric populations. The safe administration of oral suspensions requires proper shaking to ensure homogeneity prior to dosing(Neves and Auxtero, 2021; Ryu and Lee, 2012; Sobhani et al., 2008a).

The selection of the oral liquid dosage form is primarily determined by the physical and chemical properties of the active pharmaceutical ingredient (API). The classification of oral liquids is based on their physical properties, such as solutions, suspensions, and emulsions, as reported in the literature (Batchelor and Marriott, 2015; Sobhani et al., 2008b; Yin et al., 2016). Among these, solutions and suspensions are the most encountered forms in daily practice and therefore receive significant attention in formulation development and clinical use. Solutions consist of the API dissolved in a liquid vehicle, while suspensions contain insoluble particles of the API dispersed within a liquid vehicle (Chiou and Riegelman, 1971; Pouton, 2000; Tiong and Elkordy, 2009; Zhang et al., 2018). The properties of the API and the desired therapeutic outcome will influence the choice of oral liquid dosage form, whether it be a solution or suspension. The formulation scientist should carefully consider the physicochemical properties of the API, patient population, ease of administration and stability while choosing an oral liquid dosage form.

Syrups have traditionally been classified as oral liquids containing high concentrations of sugars such as sucrose. The use of these sugars in syrups has raised concerns due to their potential for inducing glycogenic and cariogenicity (Bowen and Koo, 2011; Cury et al., 2000; Leme et al., 2006; Loesche, 1986). These concerns have led to an increasing interest in the replacement of sugars in whole or in part with alternative viscosity modifiers. Cellulose ethers, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxypropyl cellulose and hydroxyethylcellulose, are non-glycogenic because they do not hydrolyze and enter the circulation (Efthimiadou et al., 2014; Park et al., 2010; Sheikholeslami et al., 2017; Zhang et al., 2013). They can serve as a syrup-like delivery system for medications meant for diabetics or others whose diets must only contain non-glycogenic foods. These cellulose derivatives have a viscosity similar to sucrose syrup and may be further modified to provide the required viscosity for a composition. These cellulose ethers can mimic the rheological properties of syrups without the risk of inducing glycogenic or cariogenicity. They are also useful in providing a consistent viscosity and texture for the oral liquid. The use of cellulose derivatives, preferably hydroxyethylcellulose, represented by brand name Natrosol™ 250 hydroxyethyl cellulose, can lead to improved patient compliance and the shelf life of the oral liquid formulation (Formulating elegant liquid and semi-solid drug products, n.d.).

Rheology, texture, and stability are the key considerations in the formulation of elegant and successful oral liquid preparations. For oral solution or suspension formulations, rheological properties such as shear-thinning and thixotropy are critical parameters that must be evaluated and controlled(Gallegos et al., 2021; de Loubens et al., 2010; Marconati et al., 2017; Mowlavi et al., 2016; Patel et al., 2020; Steele et al., 2015).Shear-thinning fluids exhibit a reduction in viscosity as the shear rate or stirring speed is increased. This feature is of paramount importance in oral solutions, syrups, and suspensions as it allows for

ease of administration through the esophagus and improved patient comfort(Gallegos et al., 2021; Letawsky et al., 2020; Meilgaard et al., 1999; Newman et al., 2016; Okonkwo et al., 2021; Ong et al., 2018). Thixotropic fluids, on the other hand, exhibit a decrease in viscosity over time when subjected to a continuous shear rate, and it takes a longer time for the fluid to regain its original viscosity once the shear rate is removed (Barnes, 1997; Bautista et al., 1999; Dullaert and Mewis, 2006; Fredrickson, 1970; Li et al., 2020; Manero et al., 2007). The viscosity and rheological properties of oral liquid formulations can be evaluated using a rheometer. Figure 1 provides a graphical representation of the rheological properties of oral liquids with respect to shear rate and time.

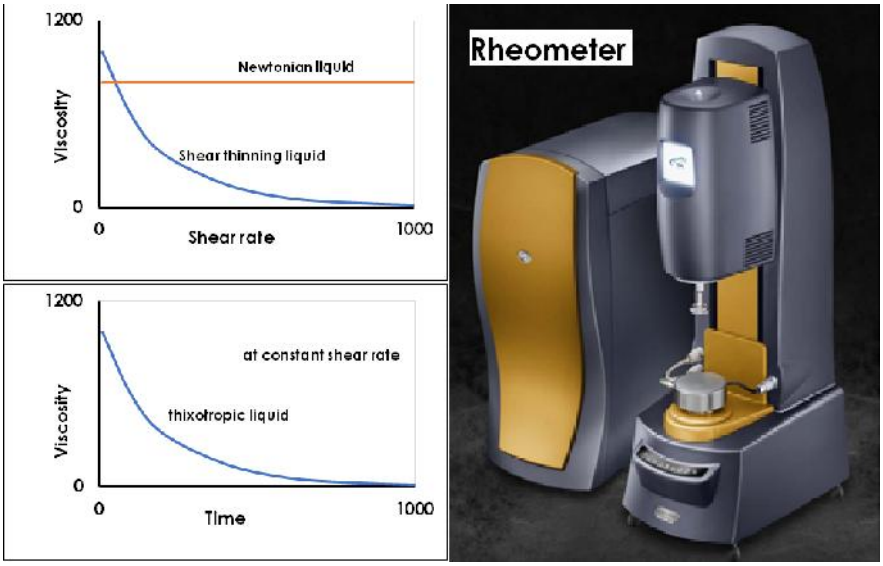

Figure 1: Typical rheological profiles of oral liquids & TA DHR rheometer

Additionally, textural properties such as consistency, firmness, hardness, and spreadability(Gao et al., 2016; Kim et al., 2014; Lin et al., 2003; Pathaw et al., 2021) are also crucial in ensuring patient acceptability and stability of oral liquid formulations. These properties can be evaluated using a texture analyzer, which measures the sensory characteristics of the systems under no-flow or shear conditions. Figure 2 provides an illustration of a typical texture analyzer and an example of analysis.

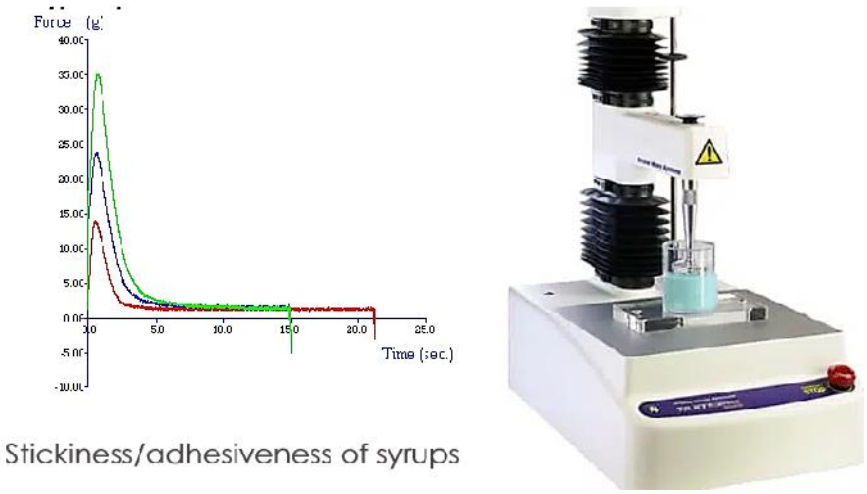

Figure 2: TA XT Plus texture analyzer typical study of syrup on the adhesiveness

2. Typical excipients used in the oral liquid dosage forms

Oral liquid dosage forms are composed of two key components: the active pharmaceutical ingredient (API) and the vehicle or continuous phase in which the API is solubilized or suspended. Water is a commonly employed vehicle in the formulation of pharmaceutical solutions and suspensions. However, in instances where the API is insoluble in water or has poor bioavailability, the target formulation is a solution, and alternative strategies such as using cosolvents, may be employed. Cosolvents such as ethanol, glycerol (85 percent), and propylene glycol can be used to solubilize the API and improve the solubility and bioavailability of the

API. The use of cosolvents should be optimized to achieve the desired solubility while minimizing any adverse effects on taste or safety. The selection of a cosolvent should be based on the solubility and toxicity profile of the API & cosolvent and on the regulatory guidelines. Additionally, the solution should also be thermodynamically stable, i.e., the API should be stable to the solvent and the solvent should not be volatile.

When the desired formulation is a suspension containing suspended API particles, additional excipients with various functionalities may be included in the vehicle to ensure a stable suspension. These excipients may include:

- Suspending agents, such as surfactants provide wetting, stabilization, and improved redispersibility of the suspended API particles.
- Thickening or rheology modifying agents, such as cellulose derivatives provide targeted rheology and control the sedimentation or settling of dispersed particles. Examples include Hydroxyethylcellulose, Hydroxypropylemethyl cellulose and Hydroxypropylcellulose.
- Flocculating agents, which help to prevent caking or hard settling of the particles and improve redispersibility.
- pH modifiers, which can be used to control the pH of the formulation and ensure the stability and solubility of the API.
- Preservatives are used to prevent bacterial or fungal contamination of the formulation.
- Flavoring agents are used to improve the taste of the formulation.
- Permitted food colors, which are used to enhance the visual appeal of the formulation.

Table 1 can provide an overview of these excipients and their basic functions in oral liquid formulations.

Table 1: Typical ingredients used in oral liquids

Category of ingredients	Name	Function
Solvents/cosolvents	Ethanol Glycerin PEG 400 Water	To solubilize the API or as media for the vehicle in suspensions or solutions.
Surfactants/suspending agents	Polysorbate 20/80 SLS Poloxamer 188/331/407 Glycerol stearate Lecithin	For wetting/dispersion and stabilization
Buffers/pH modifiers	Acetic acid Ascorbic acid Citric acid Sodium Hydroxide Sodium citrate Sodium bicarbonate	pH regulators
Thickening/viscosity modifying agents	Guar gum Xanthan gum Sodium carboxymethylcellulose Hydroxypropylcellulose Hydroxypropyl methylcellulose Hydroxyethylcellulose Povidone Sodium alginate	Viscosity modifying agents
Preservatives	Benzoic acid Butylated hydroxyanisole Propylparaben Methylparaben Sorbic acid Sodium benzoate	To avoid degradation of polymer or other ingredients.
Isotonicifier	Propylparaben Methylparaben Sorbic acid Sodium benzoate Sodium chloride Mannitol	Isotonicity regulator
Antifoam	Simethicone Dimethicone	To avoid foaming

Though there are a wide variety of excipients(GurdoganGuler et al., 2021; Lein and Ng, 2015; Renwick, 1990; Rouaz et al., 2021; Saito et al., 2022) that can be used in oral liquid formulations to impart various functionalities, the current review will focus primarily on viscosity modifiersand, more specifically on the use of hydroxyethylcellulose (HEC) polymer as a cellulose derivative excipient in oral liquid dosage forms.

2.1. Polymers used as thickening/viscosity modifyingagents.

The viscosity of the liquid is an important characteristic that affects the flowability of the oral liquid and the settling rate of the particles in suspensions. To increase the viscosity of the liquid and improve its flowability, thickening agents are often added to the formulation. Sucrose and other sugars have traditionally been used as thickening agents in oral liquid formulations due to their ability to increase the viscosity of the liquid and mask the unpleasant taste of the API. However, there is a growing trend towards the replacement of sugars with alternative thickening agents, such as cellulose derivatives, due to concerns about the glycogenic and cariogenic properties of sugars. The use of non-sugar-based thickening agents in oral liquid formulations has gained significant attention in recent years due to the growing concern surrounding the negative health effects associated with the use of high concentrations of sucrose or other sugars. Examples of these alternative thickening agents include polysaccharides such as agar, tragacanth, and gum Arabic, as well as synthetic polymers such as Xanthan gum and Carrageenan, and cellulose derivative polymers. The selection of a suitable thickening agent is dependent on the specific formulation requirements and desired properties of the final product.

Cellulose derivatives, specifically those derived from plant or wood sources, have become increasingly popular as alternative thickening agents in oral liquid dosage forms. These cellulose ether polymers, including sodium carboxymethylcellulose, hydroxyethylcellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and ethylcellulose, possess varying properties based on the type of substitution and molecular weight, making them suitable for both aqueous and non-aqueous applications in oral liquid formulations. The properties of the cellulose ethers are influenced by the degree of substitution (DS) and the average degree of polymerization (DP) which determines the viscosity, solubility, and stability of the polymer. This property makes cellulose derivatives a versatile excipient in oral dosage forms. Furthermore, cellulose derivatives, such as hydroxyethylcellulose (HEC), are non-glycogenic and do not enter the bloodstream, making them a suitable alternative for patients with diabetes or those on a non-glycogenic diet. Additionally, cellulose derivatives can help to improve the stability and shelf life of oral liquid formulations by reducing the settling rate of particles, and with commonly used preservatives, the growth of fungi and other microorganisms can be controlled.

Cellulose derivatives, however, can hydrolyze at low pH (Alessi et al., 2018; Deobald and Crawford, 1987; McCarthy, 1987; ÖZER et al., 2020; Pometto and Crawford, 1986) and therefore have a limited shelf life due to the breakdown of their polymeric chains. It is critical to evaluate the pH of the oral liquid formulations and take necessary measures to control the hydrolysis rate of cellulose derivatives, such as buffering and the use of appropriate preservatives(Kumar and Yagnesh, 2016; Lykouras et al., 2020; Rajan et al., 2022; Sharma et al., 2015).

2.2. Hydroxyethylcellulose as viscosity modifying agents in oral liquid dosage forms

Hydroxyethyl cellulose (HEC), represented by the brand name Natrosol™ 250 hydroxyethylcellulose, a popular ingredient in pharmaceutical formulations is the non-ionic, water-soluble polymer, due to its ability to provide thickening and viscosity-modifying properties(Al-Ani et al., 2021; Andrews et al., 2009; Khutoryanskiy, 2011; di Prima et al., 2021; Roy et al., 2009; Roy and Prabhakar, 2010). Its ability to increase viscosity, improve suspension stability, and mask the taste of active pharmaceutical ingredients (APIs) make it an attractive excipient for use in oral liquid formulations. HEC is also considered safe and non-toxic, as well as non-glycogenic and non-cariogenic, which makes it suitable for patients with diabetes or restricted diets(Ates, 2015; El-Naggar et al., 2020; Mahmoud et al., 2021; Sindhu et al., 2021). It belongs to the family of cellulose ethers, similar to Aqualon™ and Blanose™ sodium carboxymethylcellulose

(CMC), which are characterized by the presence of ether linkages in the cellulose backbone. As opposed to CMC, HEC is non-ionic in nature, rendering it less susceptible to pH fluctuations and greater tolerance for the presence of organic cosolvents and anionic molecules. Moreover,HEC is differingfrom other cellulose ethers like Benecel™ hydroxypropylmethylcellulose (HPMC) and Klucel™ hydroxypropylcellulose (HPC) in that itmay soluble in both cold and hot water and does not precipitate from aqueous solutions at high temperatures(Fortin and Charlet, 1989; Gray, 2020; Romo-Uribe, 2021; Shimamura et al., 1981; Werbowyj and Gray, 1980).

Cellulose is a naturally occurring polysaccharide that is composed of repeating units of cellobiose. Each cellobiose unit is made up of two anhydroglucose units, which are linked together by a glycosidic bond. The anhydroglucose units in cellulose contain three hydroxyl groups (-OH) that can react with other molecules(Calvo et al., 2021; Kadajji and Betageri, 2011; Kamel et al., 2008; Klemm et al., 2005; Li et al., 2010), as illustrated in Figure 3. Hydroxyethyl cellulose (HEC) is a cellulose ether polymer that is produced by the reaction of cellulose with ethylene oxide. This reaction results in the introduction of hydroxyethyl groups (-CH_2CH_2OH) along the cellulose chain. The hydroxyethyl groups are attached to the cellulose chain by replacing some of the hydroxyl groups (-OH) that are present in the cellulose backbone.The replacement of hydroxyl groups with hydroxyethyl groups changes the properties of the cellulose polymer(Jain et al., 2013; Klouda and Mikos, 2008). The hydroxyethyl groups are polar and therefore water-soluble, which makes HEC water-soluble as well(Santana Fagundes et al., 2016; Zhang, 2001; Zhang et al., 2001; Zhang and Chen, 2002). Additionally, the hydroxyethyl groups increase the viscosity of the polymer by creating more hydrogen bonding opportunities between polymer chains, which can increase the thickness of the solution.

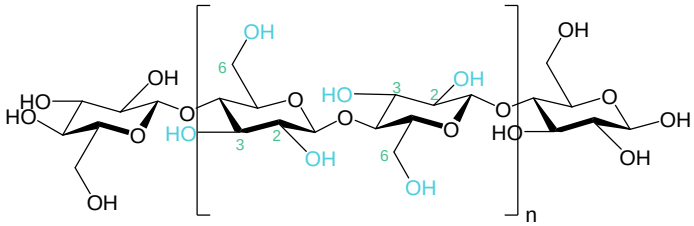

Figure 3: Structure of cellulose in chair form notation.

The viscosity-modifying properties of HEC are due to its ability to form hydrogen bonds with water molecules. The more hydroxyethyl groups in the polymer, the more hydrogen bonds can be formed and the higher the viscosity of the solution (Hussain et al., 2018; Liu et al., 2018; Olmos and González-Benito, 2021; Youssef et al., 2021). This can be adjusted by varying the degree of substitution (DS) of the HEC, which is the ratio of the number of hydroxyethyl groups to the number of hydroxyl groups in the cellulose backbone.This replacement of hydroxyl groups with hydroxyethyl groups makes the polymer water-soluble, thickening, and viscosity-modifying properties. The degree of substitution (DS) can be used to fine-tune the viscosity and thickening properties of the HEC(Garate et al., 2017; Klug, 2007; Werbowyj and Gray, 1976). The structure of Natrosol™ 250 HEC polymer is shown in Figure 4. The MS and DS of this example are 2.5 (10 ethylene oxide groups and 4 anhydroglucose units) and 1.5 (6 substituted hydroxyls and 4 anhydroglucose units), respectively.

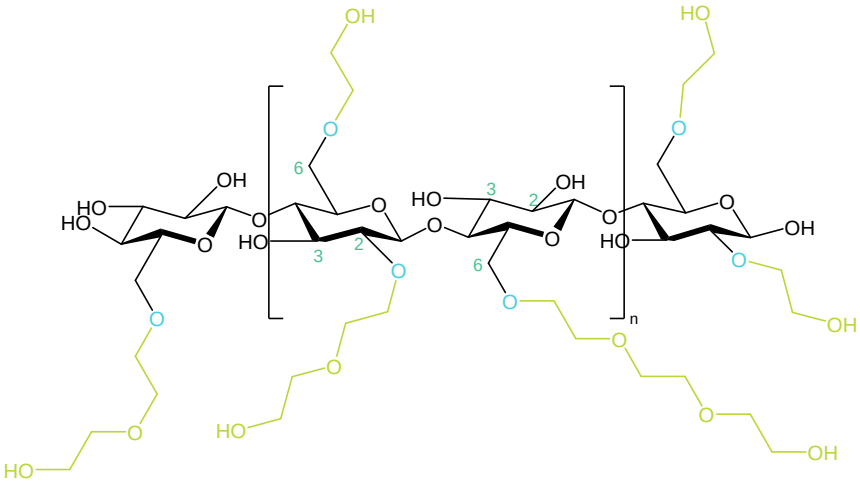

Figure 4: Idealized structure of Natrosol™ 250 HEC. This example has an MS of 2.5 (10 ethylene oxide groups/4 anhydroglucose units) and a DS of 1.5 (6 hydroxyls substituted/4 anhydroglucose units).

3. Dissolving hydroxyethylcellulose in water

Water can be used to dissolve hydroxyethylcellulose (HEC) under either hot or cold conditions. HEC's particles do, however, tend to bunch together when first combined with water, just like many other water-soluble polymers. This tendency for the particles to agglomerate is known as lumping and can affect the rate at which the polymer dissolves. Many variables, including the viscosity grade of the HEC and the rate of addition to the water, affect the amount of lumping that takes place throughout the dissolve process. Lower viscosity grades are often easier to dissolve than higher viscosity grades.

Ashland (the manufacturer) recommends below different techniques for preparing Natrosol™ 250 Pharm HEC solutions(Brady et al., 2017; Colby, 2010; di Giuseppe, 2018):

- Natrosol™ 250 Pharm HEC polymer should be gradually added into the water's turbulent vortex. In order to avoid lump formation, this approach calls for progressively adding the polymer to the water while stirring the mixture. The stirring should continue until the entire mixture is smooth and free of any remaining swelled or gelatinized particles.
- Before adding Natrosol™ 250 Pharm HEC intowater, prewet the particles with an organic liquid that is water soluble, such as glycerin, propylene glycol, or ethanol. This method can improve the solution rate by effectively separating the particles of Natrosol™ 250 Pharm HEC, preventing lump formation.
- If the formulation contains other dry excipients, then blending Natrosol™ 250 Pharm HEC with them can also improve the solution rate. This method separates the particles of Natrosol™ 250 Pharm HEC, allowing the solution to be added to water without lump formation.

In another case of highly hydrophilic cellulose derivative polymer, such as Aqualon™ and Blanose™ sodium carboxymethylcellulose (CMC), the manufacturer (Ashland) suggests using water eductor to wet the polymer particles more rapidly. In this small equipment, the polymer is fed through a funnel into the water-jet educator (FEDDERSEN and THORP, 1993; C. G. Lopez et al., 2015), where the high velocity of water instantly wets the particles without lumping. The typical equipment setup is given in Figure 5. It’s worth noting that the solution rate can be improved by some experimentations such as changing temperature, or pH, using surfactants to wet the polymer particles, and so on.

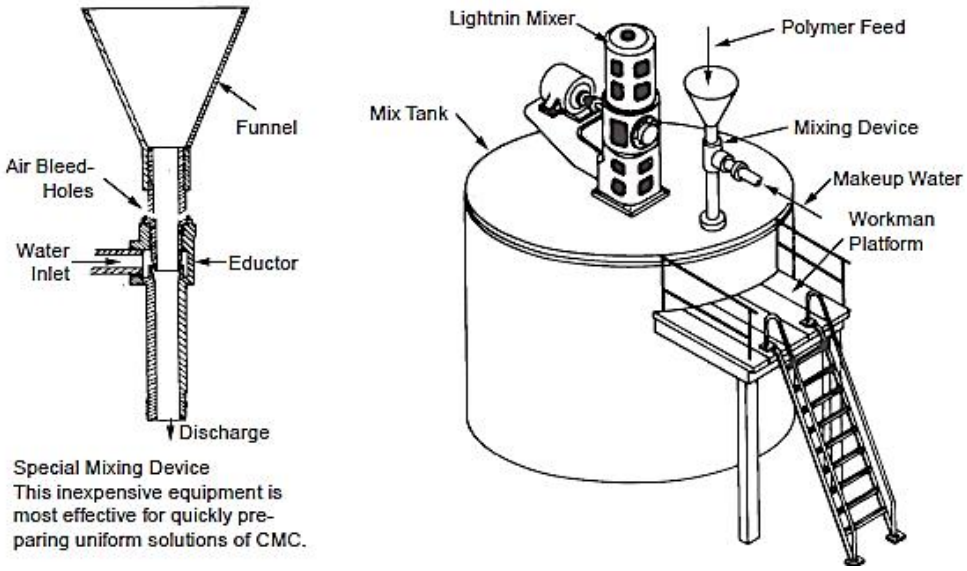

Figure 5: Typical installation of educator type device

4. Viscosity of hydroxyethylcellulose polymer

A broad variety of polymeric solutions, as well as numerous pharmaceutical liquid and semi-solid formulations behave as non-Newtonian fluids, with viscosity dependent on applied shear rate. This indicates that their viscosities are not set, but rather vary according on the amount of shear to which they are subjected. In pseudoplastic flow, also known as shear-thinning flow, the viscosity is inversely proportional to increasing shear rate and this type of flow beahaviour is the most prevalent type of non-Newtonian fluids. Natrosol™ 250 Pharm HEC solutions are examples of shear-thinning materials. As a result, even if a high-viscosity Natrosol™ 250 Pharm HEC solution seems to be viscous in a container, but when poured it might behave as a runny liquid. When the applied shear/force is removed, the viscosity soon returns to its former high level. With this tendency, Natrosol™ 250 Pharm HEC is frequently used to alter the viscosity of pharmaceutical liquid formulations. Natrosol™ 250 Pharm HEC can produce a broad range of viscosities, depending on the grade chosen and the concentration employed. As a result, solution viscosity is affected by several parameters, which will be explored in the following sections.

4.1. Effect of concentration of hydroxethycellulose on viscosity

Natrosol™ aqueous solutions exhibit increased viscosity with increasing concentration and molecular weight, as seen in in Figure 6. Many polymeric solutions have the concentration-dependent viscosity property(Dinic et al., 2022; Dinic and Sharma, 2019; Evageliou, 2020; Martínez Narváez et al., 2021; Morris, 2020). The rate of increase in the viscosity is dependent on the Molecular Weight or chain length of the polymer. For lower Molecular Weight grades, the slope or rate of increase with respect to concentration is lower, and primarily linearly dependent. However, as the Molecular Weight increases, the rate of increase in viscosity is linear up to certain amount of concentration, and after whichthe increase in viscosity is proportional to concentration to the power of a number which is typically >1. The plot between the concentration of hydroxyethylcellulosepolymer and viscosity for various molecular weights is shown in Figure 6.

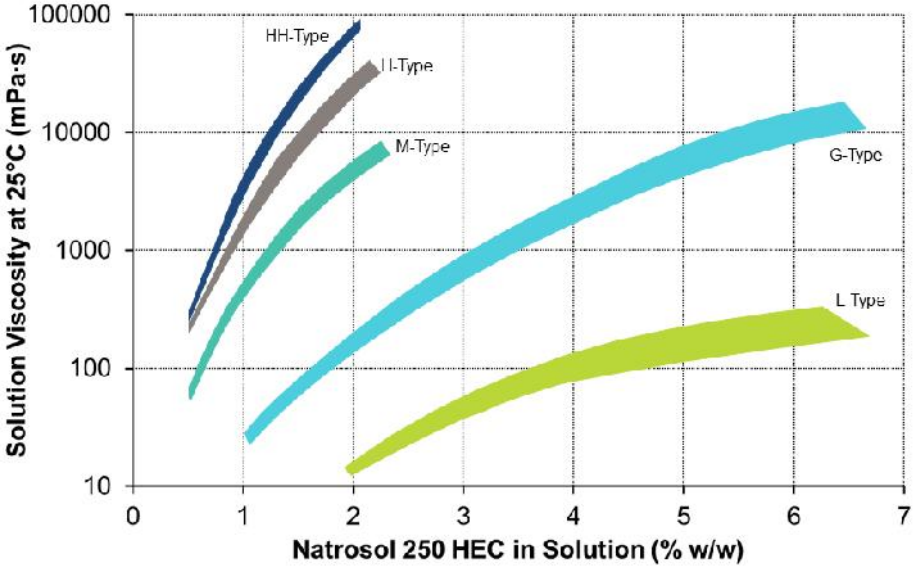

Figure 6: Effect of Concentration on Viscosity of Aqueous Solutions of Natrosol™ 250 Pharm HEC

4.2. Effect of shear rate on the viscosity of different MW grades of hydroxethycellulose

The shear rate significantly affects both the viscosity of the solution and the rheological characteristics of Natrosol™ 250 Pharm HEC. Shear rate is a measurement of the rate at which a fluid deforms or flows because of an applied force. Throughout the stages of manufacture, packing, storage over the course of its shelf life, and application, a formulation is subjected to various intensities of shear. The solution of Natrosol™ 250 Pharm HEC has shear-thinning properties (Fujii et al., 2003; Meadows et al., 1995; Różańska et al., 2014), meaning that its viscosity decreases as the shear rate increases. This may contribute to a product's need for several qualities like formulation stability or ease of applying ordispensing under pressure. It is crucial to measure viscosity throughout a variety of shear rates, which is known as a flow curve, to comprehend the effect of these shear forces on solution rheology.

Flow-wise, all grades of Natrosol™ 250 Pharm HEC act similarly, although to differing degrees as shown Figure 7. Eventually, the smaller the molecular weight, the less variation in viscosity that happens under various stress circumstances. Natrosol™ 250 Pharm HEC is also a viscoelastic material, which means it exhibits both elastic and viscous properties. When a high concentration of Natrosol™ 250 Pharm HEC is dissolvedat a high concentration, the polymer particles create a three-dimensional network that gives the solution solid-like characteristics. These polymer gels are viscoelastic because they combine the characteristics of elastic (like a solid) and viscous (like a liquid).

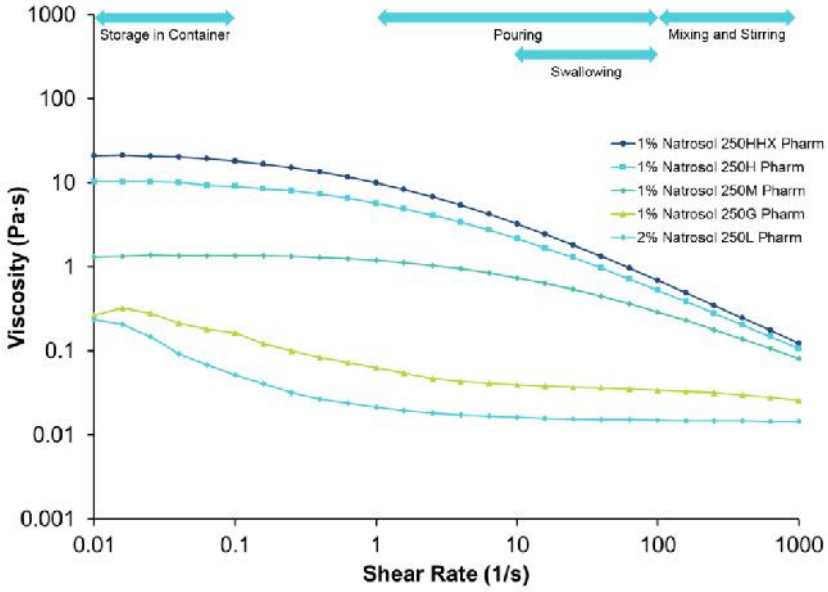

Figure 7: Viscosity as a function of shear rate for the solutions containing different grades of Natrosol™ 250 Pharm HEC Grades.

Data from measurements made in an oscillating disc rheometer at varying frequencies are displayed in Figure 8 to demonstrate the viscoelastic characteristics of aqueous gels made of Natrosol™ 250 Pharm HEC at various concentrations and molecular weights. In a typical viscoelastic system, the complex viscosity is high at low frequencies and drops monotonically as the frequency is raised.

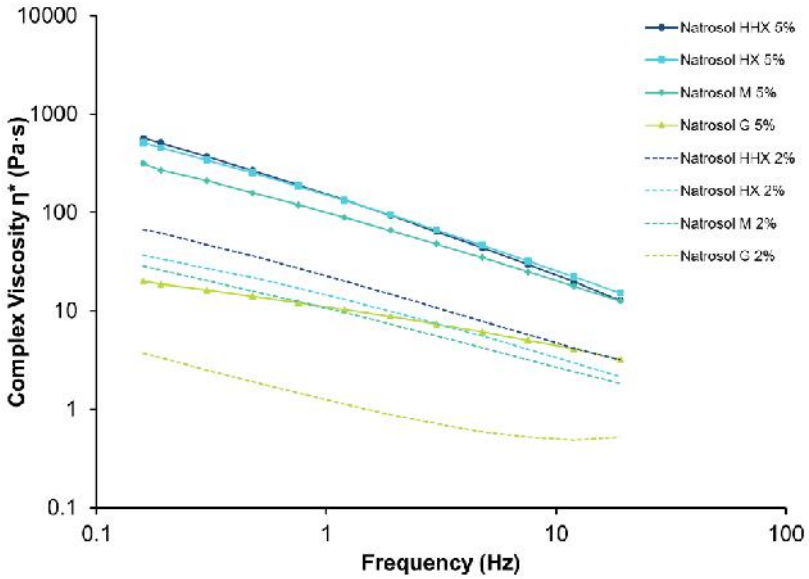

Figure 8: Effect of polymer grade, concentration, and oscillatory frequency on the viscosity of Natrosol™ 250 Pharm HEC gels

5. Suitable preservative for hydroxyethylcellulose in oral liquids

Apart from safety and regulatory considerations, there is a broader public discussion concerning the perceived safety of conserved pharmaceutical items. The public frequently disputes the necessity for preserved formulations, sometimes forgetting the serious health problems caused by non-preserved or inadequately stored medications in the past. Despite the fact that preservatives face an unclear future, it is critical that they continue to be accessible for integration into the various multi-use pharmaceutical products in order to ensure quality and patient safety. With the limited options for antimicrobial preservatives now available, as well as the years of clinical safety established, a rigorous risk-to-benefit analysis should be performed before dismissing preserved multi-dose formulations. If patient safety is to be ensured, multi-use oral, topical, and parenteral products must be preserved.

Preservatives, either alone or in synergistic combinations, are still required to avoid microbial contamination of multi-use liquid or semi-solid pharmaceutical formulations, especially from opportunistic pathogens. Serious implications for the health of the patient may arise from exclusion. There are few regulatory-approved preservatives that can be incorporated in this multi-purpose therapeutic oral liquid dose form. The ideal conditions for preservative efficacy (pH, physical and chemical stability) are rarely the same as those for the product itself, hence compromises are frequently required to maintain an acceptable product shelf-life. Review of the marketed oral liquid formulations containing hydroxyethycellulose highlights the need for the addition of preservatives to prevent the growth of microorganisms. Methyl paraben, propyl paraben, and benzyl alcohol are the most often used preservatives in marketed oral liquid formulations.

6. Commercially marketed formulations containing hydroxyethylcellulose in oral liquids.

Hydroxyethylcellulose (HEC), as a thickener, can be used to produce a viscosity similar to that of a sucrose syrup, which is useful for oral liquid formulations that are intended to mimic the viscosity of traditional syrups. Another way to create a superb facsimile of traditional syrup is to add one or more artificial sweeteners. The viscosity range of numerous evaluated commercial syrup products is shown in Figure 9's shaded area. The rheological characteristics of the examined commercial syrup formulation can be covered by a variety of grades of Natrosol™ 250 Pharm HEC with varied concentrations, according to the shear stress profiles.

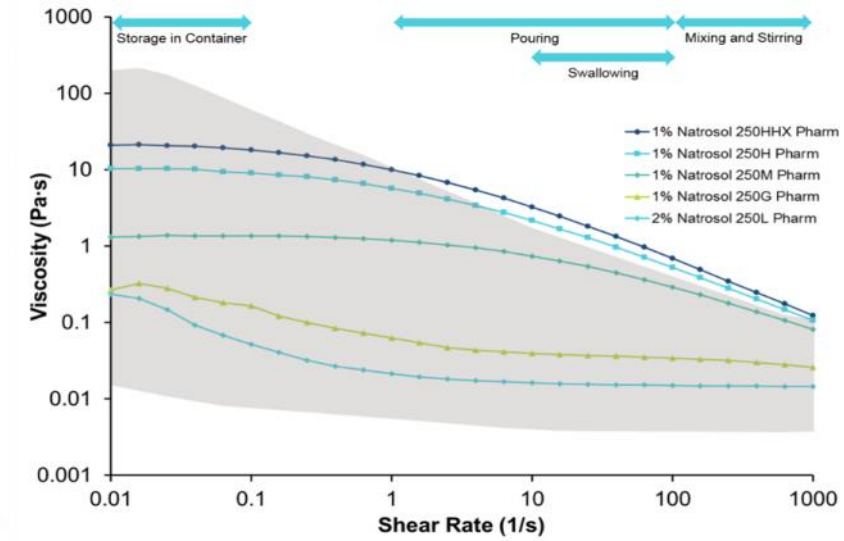

Figure 9: Effect of shear on viscosity for various Natrosol™ 250 Pharm HEC grades in relation to commercial syrups (grey area)

There are already several marketed oral liquid dosage products available in the market due to the unique benefits imparted by HEC in achieving targeted rheology/viscosity by various grades. The list of commercial products containing HEC as viscosity modifying agent is given in Table 2.

7. Potential formulations where hydroxyethylcellulose can be used as an alternative excipient

An appropriate solvent system, usually water, is used to dissolve an active pharmaceutical ingredient (API) and additional excipients in oral solutions. In oral solutions, achieving targeted viscosity/rheology of the formulation might not be a requirement for efficacy, but it can be important for patient compliance in terms of aesthetics and mouthfeel. Hydroxyethylcellulose (HEC) can be used to achieve these objectives. HEC can be used as a thickening and suspending agent in oral syrups and suspensions to achieve similar texture and suspendability as that of other sugar vehicles and viscosity modifying polymers such as xanthan gum, guar gum, carrageenan, HPMC, methylcellulose, and sodium carboxymethylcellulose.

Using HEC in oral liquid dosage formulations offers some key benefits for patient health, particularly for diabetics or those whose diet must be managed by non-glycemic ingredients. Table 3 lists few potential oral liquid formulations that can be reformulated using HEC to offer above-mentioned benefits to patient health. For example, by replacing sorbitol, saccharin sodium, and HPMC with Natrosol™ 250 Pharm HEC in Zantac oral syrup, the formulation can be completely reformulated while still achieving the targeted rheology. Similarly, Natrosol™ 250 Pharm HEC can be used to replace sorbitol, sucrose, and sugar syrup in Depakene and Zyretec to achieve an equivalent.

8. Conclusion

Hydroxyethyl Cellulose (HEC), represented by the brand name Natrosol™ 250 Pharm HEC, is a cellulose-based thickener and suspender which is commonly used in oral liquid formulations. Its unique features set it apart from other cellulose derivatives or viscosity modifying agents, making it a popular choice for formulating oral liquid dosages. One of the key advantages of HEC is that it is non-ionic in nature and is, therefore, compatible with various ions, cosolvents, and polymers that may be present in the formulation. The non-ionic nature of HEC also makes it more versatile, as it can be used in a wide range of pH values without altering its properties. In addition, the hydration of HEC is independent of pH. This makes it suitable for use in oral liquid formulations that may be unstable or prone to separation. The pH independence of HEC allows it to achieve better stability in oral liquids or suspensions, as it is not get affected by changes in the pH of the surrounding environment.

Another advantage of HEC is that it does not have cloud points at elevated temperatures. This means that it can be used in both hot and cold water, providing more flexibility in the formulation process. This allows to the production of both hot and cold water-based formulations, making it more adaptable to various product requirements. Finally, the viscosity of HEC increases with increasing concentration and molecular weight. This gives formulators wider flexibility in choosing the appropriate grade of commercially available Natrosol™ 250 Pharm HEC to achieve targeted rheology or stability in their oral liquid formulations. This feature allows for fine-tuning the final viscosity of the formulations and getting better control over the final product.

Table 2 Commercially available oral liquid dosage formulations containing HEC as viscosity modifying agent

Name of the product	Formulation dosage	Active in formulation	Inactive ingredients	Company/indication
Hemangeol	Oral solution	Propranolol HCl; 4.28 mg/mL (equivalent to 3.75 mg/mL propranolol)	Strawberry and vanilla; flavorings **Hydroxyethylcellulose;** Saccharin Sodium; Citric acid Water; preservative-free	Pierre Fabre Pharmaceuticals, Inc./ Proliferating infantile hemangioma requiring systemic therapy.
Banzel/Inovelon	Oral suspension	Rufinamide; 40 mg/ mL	MCC; Carboxymethylcellulose sodium; **Hydroxyethylcellulose;** Citric acid; Simethicone emulsion; Poloxamer 188; Methylparaben; Propylparaben; Propylene glycol; Potassium sorbate; Sorbitol solution 70% (~30% water); Orange flavor	Eisai Inc/treatment of seizures associated with Lennox-Gastaut Syndrome (LGS)
Finteplanda	Oral solution	Fenfluramine hydrochloride/ 2.2 mg/mL fenfluramine, equivalent to 2.5 mg/mL of the hydrochloride salt.	Cherry flavor; citric acid; ethylparaben; **Hydroxyethylcellulose;** methylparaben; potassium citrate; sucralose	Zogenixinc/ seizures associated with Dravet syndrome
Mobic	Oral suspension	Meloxicam; 7/5 mg/5 ml	**Hydroxyethylcellulose**; Monobasic sodium phosphate dihydrate; Raspberry flavor d9599	Boehringer Ingelheim; juvenile rheumatoid arthritis
Ferriprox	Oral solution	Deferiprone; 100 mg/mL	**Hydroxyethylcellulose**(2000 cP at 1%); Glycerin; Hydrochloric acid; Peppermint oil; Fd&c yellow no. 6; Sucralose	Apopharmainc; thalassemia syndromes
Geri-Lanta Antacid	Oral Suspension	Aluminum hydroxide,	benzyl alcohol, butylparaben,	Geri Care

Antigas		Magnesium hydroxide, Dimethicone suspension	flavor (contains alcohol), **hydroxyethylcellulose**, propylparaben, purified water, saccharin sodium, sorbitol solution	Pharmaceuticals Corp / Antacid &Antigas
Presgen B	Oral syrup	Brompheniramine maleate; Dextromethorphan hydrobromide; Phenylephrine hydrochloride	citric acid, flavor, **hydroxyethylcellulos**e, methylparaben, propylene glycol, propylparaben, purified water and sucralose	Kramer Novis / Antihistamine - Cough Suppressant - Nasal Decongestant
Geri-Lanta Supreme Cherry	Oral suspension	Calcium carbonate; Magnesium hydroxide	benzyl alcohol, flavor, **hydroxyethylcellulose**, purified water, saccharin sodium, simethicone emulsion, sorbic acid, sorbitol solution, xanthan gum	Geri Care Pharmaceuticals Corp / relieves - heartburn - sour stomach - acid indigestion - upset stomach associated with these symptoms
Dometuss	Oral syrup	Chlorpheniramine maleate; Dextromethorphan hydrobromide; Phenylephrine hydrochloride	citric acid, grape flavor, glycerin **hydroxyethylcellulose**, methylparaben, propylen glycol, propylparaben, purified water, sodiumcitrate, and sucralose.	Domel Laboratories /runny nose, sneezing, itching of the nose or throat and itchy watery eyes due to hay fever, cough
Altilan CL	Oral liquid	Chlorpheniramine maleate; Dextromethorphan hydrobromide; Phenylephrine hydrochloride	Cherry flavor, citric acid, glycerin, **hydroxyethylcellulose**, methylparaben, potassium sorbate, propylene glycol, propylparaben, purified water, sodium citrate, and sucralose	Alternative Pharmacal Corporation / Helps loosen phlegm (mucus) and thin bronchial secretions to drain bronchial tubes. Temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold.

Giltuss Children Cough and Cold	Oral solution	Dextromethorphan hydrobromide; Guaifenesin; Phenylephrine hydrochloride	citric acid, flavor, glycerin, **hydroxyethylcellulose**, methylparaben, polyethylene glycol, propylene glycol, propylparaben, purified water, sorbitol solution, and sucralose.	Gil Pharmaceutical Corp / Cough Suppressant, Expectorant, Nasal decongestant
GUAIFENESIN	Oral solution	Guaifenesin	Acesulfame K, citric acid, FD&C Green No. 3, FD&C Red No. 40, flavoring, **hydroxyethylcellulose**, purified water, sodium benzoate and sodium citrate.	Cardinal Health LLC / Helps loosen phlegm (mucus) and thin bronchial secretions to make coughs more productive.
Prednisolone Sodium Phosphate	Oral solution	Prednisolone sodium phosphate	edetate disodium, fructose, glycerin, **hydroxyethylcellulose**, methylparaben, potassium phosphate dibasic, potassium phosphate monobasic, purified water, sodium saccharin, bitter masker flavor, grape type flavor.	Amneal Pharmaceuticals NY LLC /Allergic States, Dermatologic Diseases, Edematous States, Endocrine Disorders, Gastrointestinal Diseases, Hematologic Disorders, Neoplastic Diseases, Nervous System, Ophthalmic Diseases, Respiratory Diseases, Rheumatic Disorders,
Ranitidine	Oral syrup	Ranitidine	dibasic sodium phosphate, **hydroxyethylcellulose**, methylparaben, purified water, sodium chloride, sodium saccharin, spearmint flavor, sucrose and may contain monobasic sodium phosphate.	REDPHARM DRUG INC / gastroesophageal reflux disease (GERD), gastric ulcers

Table 3: Potential few oral liquid formulations having the scope of using Natrosol™ 250 Pharm HEC

Name of the product	Formulation dosage	Active in formulation	Inactive ingredients	Company/indication
Sustiva	Oral solution	Efavirenz; 30 mg/mL	Benzoic acid, strawberry/mint flavor; medium-chain triglycerides	Bristol–Myers Squibb/HIV
Keppra	Oral solution	Levetiracetam; 100 mg/mL	Ammonium glycyrrhizinate; Citric acid; Glycerin; Maltitol solution; Methylparaben Acesulfame potassium; Propylparaben; Water Sodium citrate; Natural and artificial flavor (grape)	UCB/Antiepileptic
Zyretec	Syrup	Cetirizine HCl; 1 mg/ml	Acetic acid; Banana flavor; Glycerin Grape flavor; Propylene glycol; methyl & propylparaben; Sodium acetate; sugar syrup	Pfizer/Allergic rhinitis
Zantac	Syrup	Ranitidine HCl; 15 mg/mL	Alcohol (7.5%); Butylparaben; Sodium phosphate; HPMC; Peppermint flavor Potassium phosphate; Propylparaben. Saccharin sodium; Sodium chloride Sorbitol	GlaxoSmithKline/ treatment of ulcers, and GERD
Depakene	Syrup	Valproic acid; 50 mg/mL	Dyes; Flavors; Glycerin; Methylparaben Propylparaben; Sorbitol; Sucrose	Abbott/antiepileptic
Zovirax	Oral suspension	Acyclovir; 40 mg/mL	Methylparaben; Propylparaben; Carboxymethylcellulose sodium; Banana flavor; Glycerin; Microcrystalline cellulose; Sorbitol	GlaxoSmithKline/ antiviral (Herpes)
Tegretol	Oral Suspension	Carbamazepine; 20 mg/mL	Citric acid; Dyes; Flavors; Potassium sorbate; Propylene glycol; Sorbitol Sucrose; Xanthan gum	Novartis/Antiseizure and specific analgesic for trigeminal neuralgia

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