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A REVIEW ON PHARMACEUTICAL GRADE CELLULOSE ETHER BASED RHEOLOGICAL BEHAVIOUR EXCIPIENT SELECTION IN DRUG FORMULATION

Kausar Shafaat*[1], Dr. Vikas Kumar Singh[1], Rajnish Kumar[3], Abhishek Singh[4], Akhlaqu Rahman[5], Saurabh Kumar[6], Shalini Kumari[7], Priyanka Kumari[8]

[1]Assosiate Professor, Mahadeva Lal Schroff College of Pharmacy Aurangabad Bihar-824102.

[3-8]B. Pharm Final Year Students, Mahadeva Lal Schroff College of Pharmacy Aurangabad Bihar-824102.

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***Corresponding Author: Kausar Shafaat**
Assosiate Professor, Mahadeva Lal Schroff College of Pharmacy Aurangabad Bihar-824102.
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ABSTRACT

Pharmaceutical-grade cellulose ethers, such as hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC), are widely used as excipients due to their effects on viscosity, mechanical strength, hydration behavior, and drug release performance. In formulation development, excipient selection is commonly based on nominal viscosity grades; however, steady shear viscosity alone does not adequately describe the time dependent and deformation sensitive behavior that governs critical quality attributes and in-process performance. A comprehensive rheological evaluation of multiple HPMC and HPC grades obtained from different manufacturers was performed by preparing different concentrations of polymeric dispersions using steady shear and oscillatory rheometry. Flow sweep, amplitude sweeps, and frequency sweep analysis were conducted to characterize viscosity, viscoelastic behavior, and structural response under varying deformation conditions. All cellulose ether samples exhibited non-Newtonian, shear thinning behavior. Distinct differences in viscoelastic properties were observed between polymer types and grades. HPMC demonstrated molecular weight and concentration dependent transitions toward elastic dominated, gel like behavior, while HPC remained predominantly viscous dominated under comparable experimental conditions. The observed differences in rheological behavior highlight the limitations of relying solely on nominal viscosity grades for excipient selection. Advanced rheological parameters, particularly viscoelastic characteristics, provide deeper insight into polymer structure property relationships and their impact on formulation performance. Cellulose acetate phthalate and hydroxymethyl cellulose phthalate are also used for enteric coating of tablets. Targeting of drugs to the colon following oral administration has also been accomplished by using polysaccharides such as hydroxypropylmethyl cellulose and hydroxypropyl cellulose in hydrated form; also they act as binders that swell when hydrated by gastric media and delay absorption. This paper assembles the current knowledge on the structure and chemistry of cellulose, and in the development of innovative cellulose esters and ethers for pharmaceuticals.

KEYWORDS: Cellulose ethers, Rheology, Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, Viscosity.

1. INTRODUCTION

Rheology is the science concerned with the deformation and flow behavior of materials under applied stress or strain and provides critical insight into the structural and dynamic properties of complex systems. Depending on their molecular architecture and intermolecular interactions, materials may exhibit purely viscous behavior, purely elastic behavior, or a combination of both, referred to as viscoelasticity. Viscous materials behave as ideal liquids, undergoing irreversible deformation and dissipating applied energy as heat, with flow governed by Newton's law of viscosity, whereas elastic materials behave as ideal solids that store mechanical energy and fully recover their original shape upon stress removal in accordance with Hooke's law (Within the elastic/linear region of a material, the deformation is directly proportional to the applied force). (Gurt et al., 2024).[1]

In addition, molar substitution is particularly relevant for HPC, as it modulates thermos responsive behavior and impacts solution viscosity and phase transitions under varying temperature conditions (Palem et al., 2024).[2] The distribution of substituent groups along the cellulose backbone further affects gelation temperature, hydration rate, and microstructural development of polymer networks. Polymer concentration is another critical determinant of rheological behavior, as it governs solution structure, intermolecular entanglement density, and mechanical strength, ultimately influencing viscoelastic response and functional performance in pharmaceutical systems. During pharmaceutical manufacturing, cellulose ether based formulations are exposed to complex shear and deformation histories during processes such as blending, wet granulation, coating, compression, and dissolution. These conditions cannot be adequately characterized using steady shear viscosity measurements alone.

Viscoelastic properties critically influence tablet hydration and gel layer formation, coating uniformity, suspension stability, and drug release kinetics, particularly in modified release dosage forms. Furthermore, variations in polymer grade and manufacturer can result in significant differences in rheological behavior, with direct implications for process robustness, batch to batch consistency, and critical quality attributes (Cremer et al., 2023; Palem et al., 2025).[3,4] For many years pharmacists have been employing polymers in every aspect of their work; polystyrene vials, rubber closures, rubber and plastic tubing for injection sets, and polyvinylchloride flexible bags to hold blood and intravenous solutions are all examples of such polymers. The initial use was often restricted to packaging rather than drug delivery.

Subsequently, the amalgamation of polymer and pharmaceutical sciences led to the introduction of polymer in the design and development of drug delivery systems.

1.1 Advancements in Controlled Drug Delivery Systems

Modern drug delivery has undergone a significant transformation through the development of innovative materials, specialized excipients, and sophisticated release technologies. These advancements allow for precise control over drug liberation, transitioning from rapid to sustained release profiles. A practical benefit of this is seen in pain management: analgesics that typically require five or six daily doses can be consolidated into a single daily administration by utilizing carbohydrate-based polymer excipients.[5]

- **Polymer Classification and Matrices**

In the pharmaceutical sciences, polymers are generally categorized as either natural or synthetic. Natural polysaccharides are particularly favored for creating hydrophilic matrices, which remain a cornerstone of extended-release (ER) formulations. These systems are highly regarded due to their formulation flexibility and their ability to

provide consistent, reproducible release kinetics.[6]

❖ Understanding Drug Release Profiles

Drug release is the foundational step where a therapeutic agent exits its delivery vehicle to undergo ADME (Absorption, Distribution, Metabolism, and Excretion). This process is categorized based on the timing and intent of the delivery:

1. Immediate Release (IR): These formulations are designed for rapid dissolution, ensuring the drug is instantly available for absorption without any intentional delay.
2. Modified Release (MR): This umbrella term covers both delayed release (where the drug is liberated at a specific time after administration, such as enteric coating) and extended release (where the drug is made available over a prolonged duration).
3. Controlled Release: This includes extended-release and pulsatile-release systems, the latter of which discharges finite "pulses" of the drug at pre-programmed intervals.[7]

❖ Matrix Systems and Release Mechanisms

One of the most effective strategies for modulating drug discharge is the use of a matrix system. These are classified into three primary categories based on their chemical composition: hydrophilic, inert, and lipidic.[8,9]

The liberation of a drug from these systems is a complex interplay of the membrane's geometry, thickness, and surface area, as well as the physicochemical properties of the active ingredient. Generally, release through a non-disintegrating polymer layer occurs via three main pathways:

- Pore Diffusion: Molecules move through water-filled channels within the coating, often created by leachable components like sugars.
- Membrane Permeation: The drug partitions into the polymer coating, diffuses across the concentration gradient, and then dissolves into the surrounding aqueous environment.
- Osmotic Pumping: Release is driven by the osmotic pressure differential between the internal drug core and the external physiological environment.

❖ Key Factors Influencing Release Rates

The efficiency of a controlled-release matrix is sensitive to several variables related to the polymer and the manufacturing process:

- Polymer Characteristics: Factors such as molecular weight (viscosity), concentration, particle size, and degree of substitution significantly dictate the hydration and dissolution rates. For example, with HPMC (Hydroxypropyl Methylcellulose), the release is governed by the formation of a gel layer upon contact with gastric fluids.[10, 11]
- Processing Variables: The method of granulation (high vs. low shear), the volume of binder, granule size distribution, and the compression force applied during tableting all play critical roles in defining the final extended-release profile.

Table 1: Comparative Analysis of Tablet Matrix Systems.

Feature	Hydrophilic Matrix	Inert (Insoluble) Matrix	Lipidic (Fatty) Matrix
Primary Materials	Cellulose derivatives (HPMC, HPC), Sodium CMC, Alginates.	Polyethylene, Polyvinyl chloride (PVC), Ethylcellulose.	Carnauba wax, Stearic acid, Glyceryl palmitostearate.
Release Mechanism	**Swelling and Erosion:** Forms a gel layer upon hydration; drug diffuses through the gel.	**Diffusion:** Drug dissolves and diffuses through a network of capillaries/pores.	**Erosion and Diffusion:** Matrix slowly dissolves or allows pore diffusion based on lipophilicity.
Key Advantages	Highly flexible; easy to manufacture; excellent biocompatibility.	Maintains physical integrity; highly reproducible release profiles.	Useful for highly water-soluble drugs; low cost.
Common Uses	Standard extended-release tablets (e.g., Metformin ER).	Long-term delivery; drugs with high water solubility.	Formulations requiring moisture protection or taste masking.

❖ **Future Outlook for Polymer-Based Drug Delivery**

The evolution of polymer-based delivery systems is moving beyond static matrices toward "smart" or stimuli-responsive biomaterials. Future research is increasingly focused on polymers that can sense and respond to specific physiological triggers—such as shifts in pH, temperature, or enzyme concentrations to release medication only when and where it is needed. Furthermore, the integration of 3D printing technology in pharmaceutical manufacturing is set to revolutionize the field by allowing for the creation of intricate, personalized matrix geometries that can provide highly complex, multi-phasic release profiles tailored to an individual patient's metabolic needs.[12,13]

1.2 Cellulose: The Structural Foundation of Biopolymers

As the most prevalent naturally occurring biopolymer, cellulose serves as the primary structural component of cotton and higher plants. Its molecular architecture consists of extensive chains of anhydro-D-glucopyranose units (AGU). Within each unit, three hydroxyl groups are strategically positioned, with the exception of the terminal ends, playing a vital role in the polymer's behavior.[14]

❖ **Solubility and Chemical Versatility**

A defining characteristic of native cellulose is its insolubility in water and most standard solvents. This resistance is due to a dense network of intramolecular and intermolecular hydrogen bonds that tightly bind individual chains together.[15] Despite these solubility challenges, cellulose is indispensable in industries ranging from textiles and packaging to high-performance coatings. To overcome its natural limitations, researchers utilize chemical modification (derivatization). This process transforms raw cellulose into "cellulosics," which are:

- Reproducible and Strong: Ideal for industrial manufacturing.
- Biocompatible: Frequently used in specialized biomedical applications, such as blood purification membranes.
- Tailorable: Properties can be adjusted to meet specific engineering requirements.

❖ **Molecular and Supramolecular structure**

The functionality of cellulose is rooted in its specific molecular arrangement. The hydroxyl groups are located at the C_2 and C_3 (secondary) and C_6 (primary) positions. Furthermore, the CH_2OH side groups adopt a transgauche (tg) orientation relative to the O_5–C_5 and C_4–C_5 bonds. At a higher organizational level, cellulose exists in a semi-crystalline solid state, featuring two distinct regions:

- Crystalline Regions: Areas of high order and close packing where strong inter-chain bonding makes hydroxyl

groups nearly inaccessible to reagents.

- Amorphous Regions: Areas of low order where the structure is more open, allowing for high reactivity and accessibility.
- The Degree of Crystallinity (DP) typically ranges from 40% to 60%, depending largely on the biological source and any pre-treatments applied to the material.

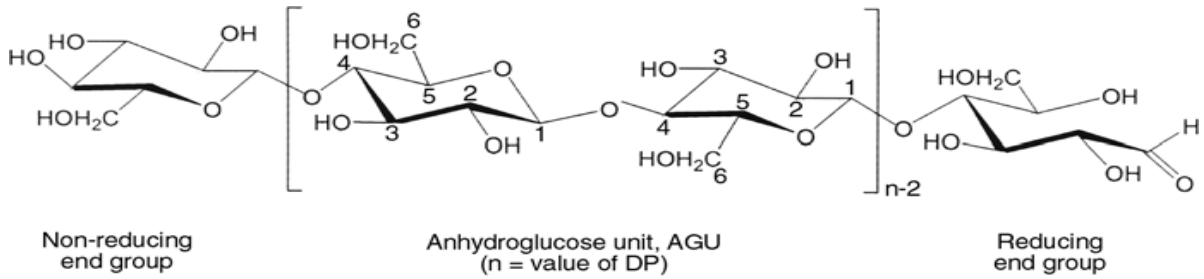

Figure 1: Molecular structure of cellulose.

Crystalline Polymorphs and Transformations

Cellulose can exist in several distinct crystalline forms, known as polymorphs, each with varying levels of thermodynamic stability.

The transition between these forms allows scientists to manipulate the physical properties of the fiber, enhancing its reactivity or mechanical strength for specific industrial uses.

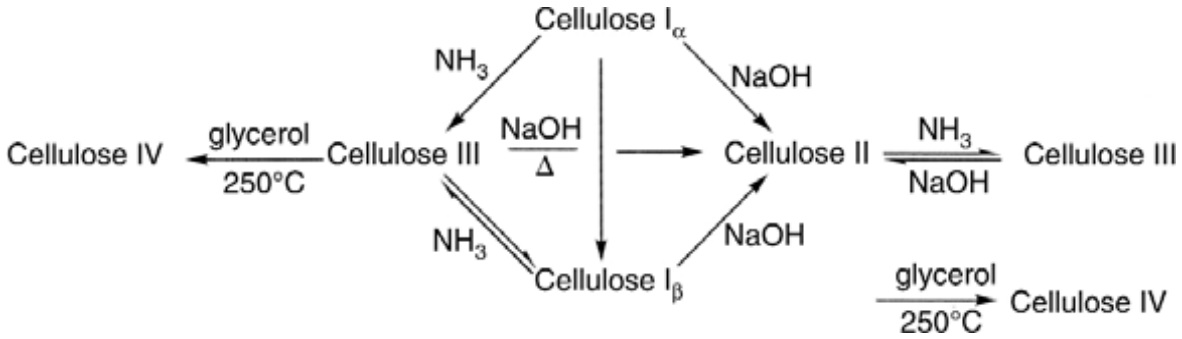

Figure 2: Transformation of cellulose into its various polymorphs.

Table 2: Comparative Analysis of Native and Treated Cellulose Crystalline Forms.

Polymorph	Description	Stability/Origin
Cellulose I	Native cellulose produced by plants.	Thermodynamically less stable than Cellulose II.
Cellulose II	Formed by treating Cellulose I with aqueous sodium hydroxide; also found in marine algae.	The most thermodynamically stable structure.
Cellulose III	Produced by treating Cellulose I or II with liquid ammonia.	Intermediate crystalline form.
Cellulose IV	Generated by heating Cellulose III.	High-temperature derivative.

2. Chemical Derivatization of Cellulose

The chemical modification of cellulose is primarily targeted at the three reactive hydroxyl groups (–OH) located on each anhydroglucose unit. By substituting these groups, the strong hydrogen-bonding network is disrupted, allowing for drastic changes in solubility, thermoplasticity, and chemical reactivity.

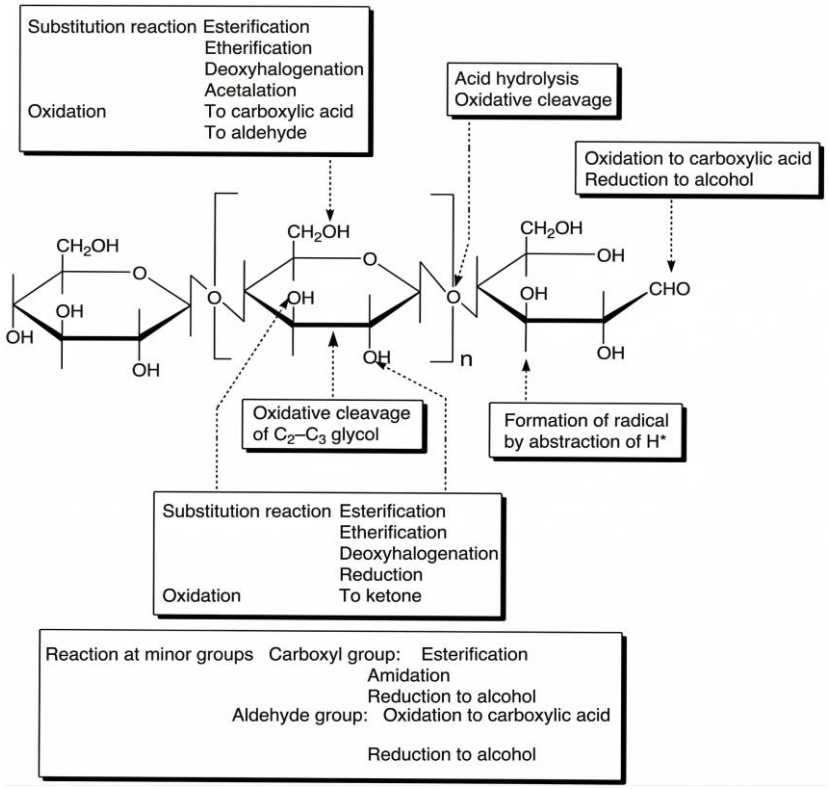

Figure 3: Position in cellulose structure for chemical modifications.

❖ Functionalization via Substitution

The most industrially significant modifications are esterification and etherification. These reactions are the standard pathways for producing derivatives that are soluble in water or organic solvents.

- Etherification: This involves the reaction of cellulose with organic halides or epoxides (e.g., methyl chloride or ethylene oxide) in an alkaline medium. Common examples include Methylcellulose (MC) and Hydroxypropyl Methylcellulose (HPMC), both of which are essential in the pharmaceutical matrix systems we discussed earlier.
- Esterification: Cellulose reacts with organic or inorganic acids (or their anhydrides). Notable derivatives include Cellulose Acetate (CA), used in membranes and fibers, and Cellulose Nitrate, used in coatings.

❖ Alternative Modification Pathways

While substitution is the most common, other specialized techniques allow for the creation of high-performance biomaterials:

- Grafting (Ionic and Radical): This involves attaching polymer chains to the cellulose backbone. It is often used to add new properties like antimicrobial activity or increased mechanical strength to natural fibers.
- Oxidation: Specifically targeting the C_6 primary hydroxyl or the C_2/C_3 secondary hydroxyls to introduce carboxyl or aldehyde groups. Carboxymethyl cellulose (CMC) is a prominent example of an oxidized/etherified derivative.
- Deoxyhalogenation and Acetalation: These are more niche chemical transformations used to introduce halogens or acetal functional groups, often as intermediates for further synthesis.

❖ Reactivity and Regioselectivity

The position of the modification is critical. Due to the supramolecular structure of cellulose, reagents typically attack the C_6 primary hydroxyl group first due to lower steric hindrance, followed by the C_2 and C_3 secondary hydroxyls.

Table 3: Impact of Substitution and Grafting on the Physicochemical Properties of Cellulose.

Modification Type	Reagent Example	Key Property Change
Etherification	Alkyl halides / Epoxides	Increased water solubility, thermal stability.
Esterification	Acid anhydrides	Organic solvent solubility, thermoplasticity.
Oxidation	Sodium periodate / TEMPO	Introduction of negative charge, bio-reactivity.
Grafting	Acrylic monomers	Enhanced surface functionality, hybrid properties.

2.1 Oxidized Celluloses (Oxycelluloses)

Oxidized celluloses are typically water-insoluble materials generated through the reaction of native cellulose with specific oxidants. Common agents include gaseous chlorine, hydrogen peroxide, nitrogen dioxide (N_2O_4), and periodates.

The resulting chemical profile is highly dependent on the oxidant used and the reaction environment. These "oxycelluloses" may incorporate several new functional groups alongside the existing hydroxyls:

- Carboxylic Acid groups
- Aldehyde functionalities
- Ketone groups

2.2 Microcrystallization and the Production of MCC

Microcrystalline Cellulose (MCC) is a partially depolymerized form of cellulose. It is traditionally manufactured by treating high-purity cellulose pulp with mineral acids to induce controlled hydrolysis.

- Mechanism of Action: During this process, the acid specifically attacks the β(1–4) glycosidic bonds. This breaks the acetal linkages, effectively shortening the polymer chains and reducing the Degree of Polymerization (DP) to typically less than 400.
- Sources: While wood pulp and cotton are standard, sustainable research has expanded to include bamboo, agricultural residues (rice straw, bagasse), and even newsprint waste.
- Oxidative MCC: Interestingly, using specific agents like HNO_3 or N_2O_4 not only reduces the chain length but also introduces carboxyl groups, creating a multifunctional MCC derivative.

Table 4: Comparative Analysis of Cellulose Oxidation and Microcrystallization.

Process	Primary Reagents	Structural Impact	Functional Groups Added
Oxidation	H_2O_2, N_2O_4, Periodates, Hypohalites	Shortens average chain length; often water-insoluble.	Carboxylic acid, Aldehyde, Ketone groups.
Acid Hydrolysis (MCC)	Mineral acids (HCl, H_2SO_4)	Breaks β-(1–4) glycosidic bonds; DP < 400.	Maintains original hydroxyl groups.
Oxidative Hydrolysis	HNO_3 or N2O_4	Simultaneous chain shortening and functionalization.	Carboxyl groups (Acidic MCC).

This table highlights how different processing methods impact the structural integrity and functional groups of the cellulose chain.

2.3 Etherification Mechanisms

Etherification is one of the most versatile methods for converting cellulose into functional industrial polymers. The general chemical transition can be represented as:

ROH + R'Cl → ROR' + HCl

Where ROH represents one of the three hydroxyl groups in an AGU, and R' is an organic radical (e.g., methyl, ethyl, or hydroxyethyl).

❖ Industrial Preparation

Cellulose ethers are typically synthesized by reacting alkali cellulose with reagents such as alkyl halides, alkene oxides, or activated unsaturated compounds. Key examples include:

- Methylcellulose (MC) & Ethylcellulose (EC): Prepared using methyl or ethyl chlorides/sulfates.[16]
- Mixed Ethers: Derivatives like Ethylhydroxyethyl cellulose are produced by adding two reagents (e.g., ethyl chloride and ethylene oxide) either simultaneously or sequentially.

❖ Control of Physical Properties

The final characteristics of these ethers—particularly their solubility and viscosity—are precisely controlled by two factors:

- The Molar Ratio: The proportion of the different etherifying agents used.
- Degree of Substitution (DS): The average number of hydroxyl groups replaced per AGU.

Table 5: Etherification Reagents, Co-products, and Industrial By-products.

Derivative Type	Etherifying Agent (R′)	Common Co-products/By-products	Industrial Example
Methyl Ether	Methyl Chloride (CH_3Cl)	Sodium Chloride (NaCl), Methanol	Methylcellulose (MC)
Ethyl Ether	Ethyl Chloride (C_2H_5Cl)	NaCl, Ethanol	Ethylcellulose (EC)
Hydroxyethyl Ether	Ethylene Oxide	Polyethylene glycols	Hydroxyethyl cellulose (HEC)
Mixed Ethers	Ethyl Chloride + Ethylene Oxide	Mixed salts and alcohols	Ethylhydroxyethyl cellulose (EHEC)

❖ Influence of Degree of Substitution (DS) on Solubility

The solubility of cellulose ethers is primarily governed by the balance between the hydrophobic nature of the substituent groups and the disruption of the native cellulose hydrogen-bonding network. As the DS increases, the polymer typically transitions through three solubility phases: alkali-soluble, water-soluble, and finally organic solvent-soluble.[17,18]

Table 6: Solubility Profiles of Common Cellulose Ethers Based on DS.

Cellulose Ether	Degree of Substitution (DS)	Solubility Characteristics
Methylcellulose (MC)	0.1 – 1.1	Soluble in 6–8% NaOH
	1.4 – 2.0	**Soluble in H_2O**
	2.4 – 2.8	Soluble in organic solvents
Ethylcellulose (EC)	0.8 – 1.7	**Soluble in H_2O**
	2.4 – 2.8	Soluble in organic solvents
Sodium Carboxymethyl Cellulose (NaCMC)	0.1 – 3.0	**Soluble in H_2O**
Carboxymethyl Cellulose (CMC)	0.05 – 0.25	Soluble in 6–8% NaOH
Hydroxyethyl Cellulose (HEC)	0.11 – 0.31	Soluble in 6–8% NaOH
	0.66 – 1.66	**Soluble in H_2O**
Hydroxypropyl Cellulose (HPC)	0.15 – 0.35	Soluble in 6–8% NaOH
	3.5 – 4.5	**Soluble in H_2O**
Ethylhydroxyethyl Cellulose (EHEC)	0.68 (Et) / 0.87 (HE)	**Soluble in H_2O**
	1.9–2.2 (Et) / 0.35–0.65 (HE)	Soluble in organic solvents
	1.33 (Et) / 0.51 (HE)	Soluble in both H_2O and organic solvents

- Low DS Range (0.05 – 0.35): At these levels, the substitution is insufficient to break all inter-chain hydrogen bonds. Consequently, the material only dissolves in aggressive media like 6–8% NaOH, which provides the necessary alkalinity to swell the crystalline regions.
- Intermediate DS Range (0.66 – 2.0): This is the "sweet spot" for most pharmaceutical applications. The substitution is high enough to allow hydration and water-solubility, making these polymers ideal for the hydrophilic matrix systems used in controlled drug delivery.
- High DS Range (>2.4): At high levels of substitution (especially with ethyl or methyl groups), the polymer becomes increasingly non-polar. This shifts the solubility away from water and toward organic solvents, which is useful for specialized coating applications and moisture barriers.

3. Pharmaceutical uses of cellulose and cellulose derivatives

Oxidized cellulose (oxycellulose) is cellulose in which some of the terminal primary alcohol groups of the glucose residues have been converted to carboxyl groups. Therefore, the product is possibly a synthetic poly-anhydro-cellobiuronide and that contain 25% carboxyl groups are too brittle (friable) and too readily soluble to be of use. Those products that have lower carboxyl contents are the most desirable.[19]

The oxidized cellulose fabric, such as gauze or cotton, resembles the parent substance; it is insoluble in water and acids but soluble in dilute alkalis. In weakly alkaline solutions, it swells and becomes translucent and gelatinous. When wet with blood, it becomes slightly sticky and swells, forming a dark brown gelatinous mass. So, it is used in various surgical procedures, by direct application to the oozing surface except when used for homeostasis, it is not recommended as a surface dressing for open wounds The oxidized cellulose product readily disperses in water and forms thixotropic dispersions. Such suspensions/dispersions, which may be optionally combined with other pharmaceutical and cosmetic adjuvants, can be used for producing novel film- forming systems. A wide variety of solid (crystalline or amorphous) and liquid (volatile or non-volatile) acidic, neutral, and basic bioactive compounds can be entrapped/loaded in such systems, thereby producing substantive controlled and/or sustained release formulations, having unique applications in the development of variety of cosmetic, pharmaceutical, agricultural, and consumer products. Topical formulations (cream, lotion, or spray) prepared using the oxidized cellulose material, are bioadhesive, can be applied on the human skin or hair, can be included in cosmetics. Oxidized cellulose dispersion uses in anti-acne cream, anti-acne lotion, sunscreen spray, anti-fungal cream also.

3.1 Cellulose ether

Cellulose ethers are widely used as important excipients for designing matrix tablets. On contact with water, the cellulose ethers start to swell and the hydrogel layer starts to grow around the dry core of the tablet. The hydrogel presents a diffusional barrier for water molecules penetrating into the polymer matrix and the drug molecules being released.

❖ **Sodium Carboxymethyl Cellulose (NaCMC)**

Sodium Carboxymethyl Cellulose (NaCMC) is a cost-effective, water-soluble, and polyanionic polysaccharide. Due to its unique rheological properties, it has become a preferred excipient across the pharmaceutical, cosmetic, and biomedical industries. Its primary roles include acting as a thickener, stabilizing agent, binder, and film-former.

❖ **Biomedical and Therapeutic Innovations**

Beyond its traditional use as an emulsifier, NaCMC has shown significant promise in specialized medical treatments:

- Surgical Recovery: It is utilized to prevent postsurgical soft tissue and epidural scar adhesions, acting as a physical barrier during the healing process.
- Edema Management: Gels based on CMC and Hydroxyethyl Cellulose (HEC) are highly effective water absorbents for treating various types of edemas.
- Enzyme Delivery: NaCMC hydrogels are used to deliver Superoxide Dismutase (SOD). This enzyme is naturally prone to rapid clearance and inactivation; however, when formulated as SOD-CMC conjugates or encapsulated in hydrogels, its stability and therapeutic window are significantly extended through controlled release.

❖ **Fundamentals of Cellulose Ether Rheology**

Pharmaceutical grade cellulose ethers (like HPMC, MC, and NaCMC) are categorized primarily by their nominal viscosity, which is a direct reflection of their molecular weight. When these polymers hydrate, they transition from a solid state to a viscoelastic gel.[20]

1. The Sol-Gel Transition and Thermal Gelation

A unique rheological property of non-ionic cellulose ethers (MC and HPMC) is inverse thermal gelation. Unlike most substances that thin when heated, these polymers form a firm, three-dimensional gel network at body temperature (37^{o}C).

- At Low Temperatures: Polymer chains are fully solvated by water molecules (the "sol" state).
- At High Temperatures: The water sheath is lost, leading to hydrophobic polymer-polymer interactions that result in a firm gel (the "gel" state).

2. Viscosity Grades and Formulation Impact

The selection of a "High" vs. "Low" viscosity grade is the most critical decision in designing a controlled-release matrix. Higher molecular weight polymers create a more entangled network, leading to a "tougher" gel layer that slows drug diffusion.

Table 7: Selection Criteria Based on Viscosity Grade and Molecular Weight.

Viscosity Grade (e.g., HPMC)	Molecular Weight (Mw)	Rheological Behavior	Primary Formulation Role
Low (5 – 100 cP)	Small chains	Rapid hydration; thin, easy-to-rupture film.	Tablet film coating; Binder for immediate release.
Intermediate (4,000 cP)	Medium chains	Moderate swelling; consistent diffusion barrier.	Sustained-release (SR) for moderately soluble drugs.
High (15,000 – 100,000 cP)	Long chains	Slow hydration; thick, highly viscous, and stable gel layer.	Extended-release (ER) for highly water-soluble drugs.

3. Flow Behavior: Pseudoplasticity (Shear-Thinning)

Most pharmaceutical cellulose solutions exhibit pseudoplastic (shear-thinning) flow. This means that as the "shear stress" (force applied during mixing or pumping) increases, the apparent viscosity decreases.

- In the Bottle: The liquid remains thick and stable, preventing particles from settling (excellent for suspensions).
- During Manufacturing: When pumped through a nozzle or pipe, the high shear reduces the viscosity, making the liquid easier to process without clogging machinery.[21]

4. Selection Framework for Drug Delivery Systems

Excipient selection is rarely based on the polymer alone; it must be matched to the physicochemical properties of the active pharmaceutical ingredient (API).

Table 8: Excipient Selection Decision Matrix.

API Solubility	Recommended Cellulose Ether	Selection Rationale
Highly Soluble (e.g., Metformin)	High Viscosity HPMC (K100M)	Requires a very dense, viscous gel to prevent rapid "leaching" of the drug.
Poorly Soluble (e.g., Nifedipine)	Low Viscosity / HPMCAS	Often used in solid dispersions to maintain the drug in an amorphous state for better absorption.
pH-Dependent (e.g., Aspirin)	NaCMC or Phthalate derivatives	Leverages polyanionic charge to prevent release in the acidic stomach (low pH).
Acid-Sensitive	Ethylcellulose (EC)	Provides an water-insoluble, pH-independent diffusion barrier.

The "ideal" excipient provides a balance between Rate of Hydration (how fast the gel forms) and Gel Strength (how well the gel resists erosion).[22,23] If the gel forms too slowly, the drug may experience a "burst release." If the gel is too weak, the tablet may disintegrate prematurely in the gastrointestinal tract.

CONCLUSION

Chemical modification of cellulose is performed to produce cellulose derivatives (cellulosics) which are in general strong, low cost, reproducible, recyclable and biocompatible, so they can be tailored for pharmaceutical applications. Cellulose derivatives are often used to modify the release of drugs in tablet and capsule formulations and also as tablet binding, thickening and rheology control agents, for film formation, water retention, improving adhesive strength, for suspending and emulsifying.

MCC is used as diluent and disintegrating agent for release oral solid dosage. HEC and HPC are used in hydrophilic matrix systems, while EC can be used in hydrophobic matrix system. Also, liquid and semi-solid pharmaceutical dosage forms are impor- tant physicochemical systems for medical treat- ment which require rheological control and stabilizing excipients as essential additives, CMC can be used to adjust the viscosity of syrups.

In non-solid formulations, the rheological control provided by CMC and its derivatives is indispensable. These polymers offer pseudoplastic (shear-thinning) flow, which ensures that syrups and suspensions remain stable and uniform during storage but pour easily during administration. Their film-forming and bioadhesive nature further extends their utility to topical and mucosal delivery, where prolonged contact time is necessary for therapeutic efficacy.

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