

Polymer Properties and Characterization

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7.1 INTRODUCTION

The introduction of polymer excipients has been crucial in advancing modern formulation design and solid oral drug delivery technologies over the past 50 years. Polymeric materials are widely used in a broad range of pharmaceutical products and constitute essential components of modern solid oral dosage forms. Therefore, it is important to understand polymer properties and characterization methods in order to enable rational design and development of oral solid drug delivery systems and manufacturing processes.

The word “polymer” is derived from the Greek πολυ (*polu*) for “many” and μέρος (*meros*) for “part,” meaning a long-chain consisting of many parts. The combination of repeating units to form long chains with widely variable length and structure is essential in determining the properties and applications of the resulting polymers, as the diversity of polymer properties is attributed to the simple fact that each polymer molecule consists of many parts with individual variations in sequence of repeating units and chain length.

In contrast to substances comprised of small molecules that are well defined and identified by a set of system variables, including basic physical properties, states, or characteristics with unique and discrete values, polymers are less well defined or characterized in the conventional sense. This applies to even the simplest of polymeric systems. For example, substances comprised of small molecules have a distinct molecular weight, with each molecule having exactly the same nominal mass, neglecting, for the moment, the multiple natural isotopes possible for the atomic constituents. Polymers, on the other hand, are characterized by a diverse population in which there is a broad

distribution of molar masses across the entire chain population. This is well known and clearly understood, since polymers are simply chains of many monomeric residues covalently linked together. For small molecules, it can be clearly defined if a molecule is in solution or not. Such a clear distinction may not be applied to polymers. It is quite possible for extended segments of a long polymer chain to effectively reside in bulk solution, while other parts still reside in a bulk polymer solid phase. Conceptually, the polymer chain is not completely in solution, yet the behavior of this system is clearly very different from the one where an unswollen polymer sample is sitting unsolvated in a sea of solvent. The state of an unswollen polymer is not a fluid or solution by traditional definition. Distributions in properties, states, and characteristics are what set the behavior of many polymers apart from small molecules in general. Understanding the operational impact of this difference is the first step in rational characterization and applications of polymeric materials.

This chapter will emphasize some of the pragmatic consequences of continuous distributions in composition, molecular weight, and molecule state in the use of polymeric materials and the impact on their functionality. Since the basic literature of polymer chemistry is readily available,^{1–6} we will strive not to duplicate that information here. Rather, this chapter should be viewed as an operational entry point into the practical utilization of polymeric materials. While we will attempt to maintain a firm foot in fundamental science, each of the major subsections of this chapter could constitute a monograph in its own right. As such, the approach taken is to cover the information that will be of immediate value to a user of polymeric excipients. This necessitates a somewhat limited but focused scope of coverage. In addition, we do not wish

to be distracted by equations that only approximately describe the major features of polymeric systems and often obscure important underlying operational principles. Where possible, we will resort to experimental rather than theoretical examples to illustrate specific points. Our objective is to provide the user and formulator of polymeric materials an operational and pragmatic guide upon which to base formulation decisions and understand the molecular origins of these performance metrics.

In this chapter, we will consider basic structural issues surrounding polymeric materials. One general aspect to appreciate is that two samples with identical average molecular weight and composition may display very different behavior in specific applications. Since a polymer is comprised of chains of monomer units, the total number of monomers per chain (ie, the molecular weight), the gross topology of the chain (linear vs branched), and the microstructural monomer sequence within and across the chains (ie, block A–B copolymer vs random A–B copolymer vs a physical mixture of polymers A and B, see Fig. 7.1) all impact the final properties of the material.

Determination of the average monomer composition and molecular weight of a polymeric sample are experiments routinely carried out using a variety of well-known techniques. Other attributes of polymeric materials, for example, branching or large-scale composition heterogeneity across chains, may require some level of experimental finesse but can be addressed in

broad terms. However, detailed questions regarding monomer sequencing within chains can be all but impenetrable in most instances and often require appeal to indirect challenge/response using experimental probes to even qualitatively address them. This fine detail is of significant importance in current research, since key performance properties can often be directly related to this elusive structural parameter.

7.1.1 Definition, structure, and nomenclature

The gross architecture of a polymer chain can be readily assessed by asking whether the chain or chain assembly can be mapped onto a one- (linear), two- (branched), or three- (cross-linked network) dimensional object (Fig. 7.2). In general terms, these distinctions reflect the natural spatial connectivity imparted by these chains when placed into a volume element, either in formal solution, a melt, or the solid state.

How a polymeric chain mechanically couples to and transports within a medium comprised of either other polymeric materials or low molecular weight solvent is determined in part by the gross topology of the chain system. Ultimately, the key physical attributes are the length, scale, and nature of connectivity between volume elements in solution, gel, melt, or solid states and how that connectivity propagates through space.

If one takes a linear chain and stretches it, a simple line is obtained. By the same token, the lowest

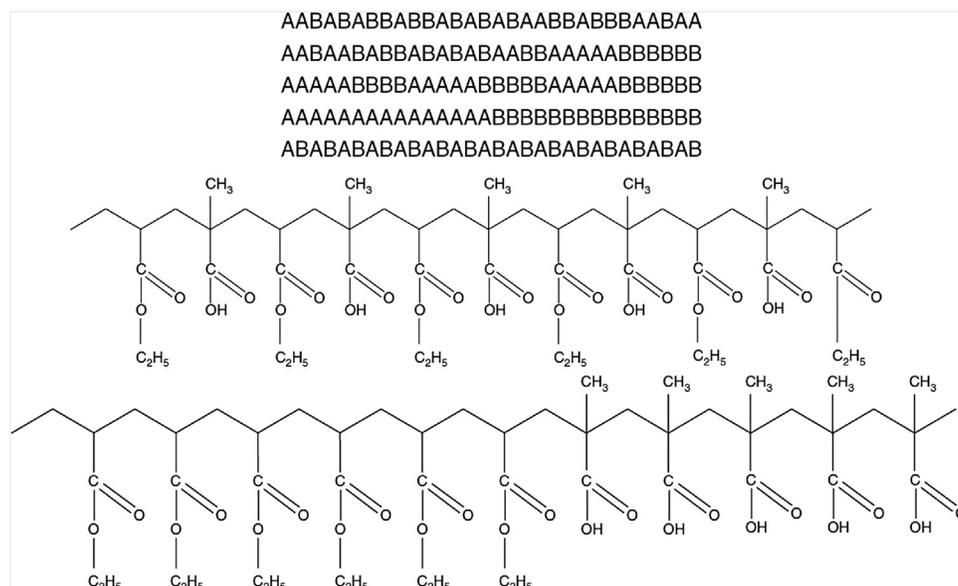


FIGURE 7.1 Examples of AB type copolymers in which the composition is the same (50:50 A:B), but the sequence of A and B monomers differ. Prototype copolymer structures shown top to bottom represent random, block graft, multiblock, diblock, and alternating AB copolymer systems. As a specific chemical example, consider the case of a 50:50 copolymer comprised of ethyl acrylate and acrylic acid as either an alternating, or diblock, architecture. The solution properties of these two materials, which have equal composition and molar mass, would be expected to be vastly different, as would solid state and melt properties.

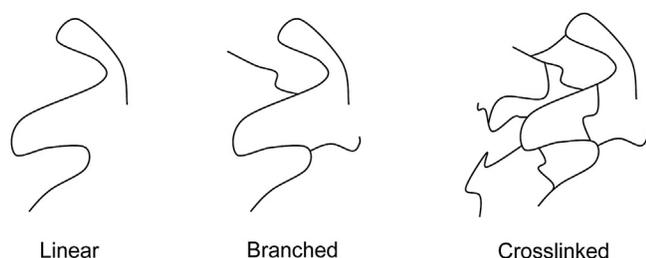


FIGURE 7.2 Diagrammatic examples of prototype chain architectures. A linear chain has been depicted as a random coil, although rigid or semirigid rods are also possible. The branched example is comprised of a main backbone with two extended long-chain branches, while more extensive branching and linking to other main backbones have been used to depict a typical cross-linked polymeric system.

dimensional object that a simple branched structure will yield under deformation, in the simplest case, is a two-dimensional planar object. A cross-linked network will yield a three-dimensional volume element under any applied deformation. In this sense, these three classes of chains are topologically and dimensionally distinct. As in any discussion involving polymeric species, the evolution between types is continuous rather than discrete even when involving dimensional extent; simple characteristics, lengths, scales along principle axes are critical.

For example, as a simple linear chain is grafted with an increasingly long side chain in the midsection of the molecule, the evolution from a purely linear to a branched planar structure occurs in a continuous fashion. Likewise, as multiple chains having a two-dimensional architecture receive additional grafts on side chains, a similar transition from two- to three-dimensional character occurs. It is critical to appreciate that even aspects that appear firmly rooted in discrete representations, dimensionality in this example, may take on some attributes of a continuous variable if viewed from specific contexts.

The chain types shown in Fig. 7.2 are assumed to represent covalently linked permanent structures. Polymeric materials of a given intrinsic topology may also assume a higher apparent dimensionality via dynamic self-association. This association can involve either similar or compositionally distinct partners. Both types of examples exist in use, with self-association of a hydrophobically modified polymer⁷ reflecting the former case, while the interaction of xanthan and locust bean gum or sodium carboxymethyl cellulose and hydroxyethyl cellulose are examples of the latter.⁸ Finally, simple physical entanglements at high polymer concentrations can be viewed as a type of dynamic cross-link, since many of the essential properties of cross-linked systems (structural robustness, high elasticity, slow transport of polymer, and/or constituent

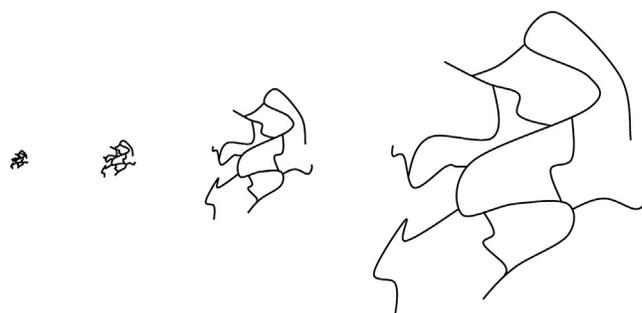


FIGURE 7.3 Depending upon the length and the flexibility of chain segments between covalent cross-links, a cross-linked polymer may be a very rigid and nonswelling solid (short, rigid segments between cross-links) or very highly swelling (low cross-link density between very flexible and solvent compatible segments) under the appropriate solvent conditions. In some cases, for example with a change of pH from highly acid to neutral or basic for a cross-linked polyacrylic acid system, conversion between collapsed and highly swollen states is readily and reversibly accomplished.

polymer) will be achieved, particularly at relatively short timescales (minutes to hours).

Gross chain topology has an influence on the flow and mechanical properties of polymer melts and solutions, as well as over the timescales of structural relaxation. In general, as a system transitions from pure linear to highly cross-linked, the balance between the viscous and elastic nature of a solution or melt tends towards more elastic. This transition is similar in kind to that observed as the molecular weight of a polymer is increased. In terms of gross phenomenology, the basic causes are tied to similar origins, with the understanding that in a cross-linked or branched polymer sample permanent covalent linkages dominate the situations, while with high-molecular-weight linear polymers dynamic interchain entanglements, which can be akin to a transient cross-link, control system response.

In addition to extensively cross-linked pure polymer systems, an intermediate type of system is exemplified by cross-linked swellable microparticulates—the most common of these being provided by cross-linked acrylic acid-based systems prepared in a microparticulate form. These are often used to control the flow properties of systems by simply encapsulating substantial fractions of the total system volume but keeping it segregated into rather small length scale packets (see Figs. 7.3 and 7.4). With large swelling ratios, relatively small amounts of particulate mass can basically encapsulate large volumes of liquid. This is often useful to build in a yield stress while maintaining a relatively low-shear viscosity, since the propagation of shear forces is basically constrained to simple soft sphere hydrodynamic effects (vs chain entanglement for a molecular dissolved system), with a net length

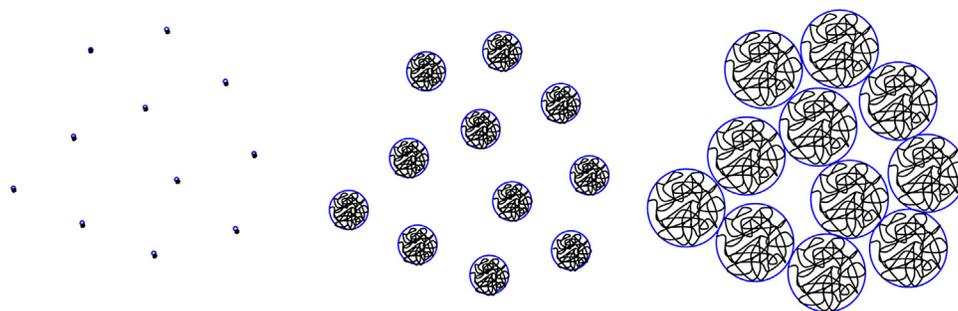


FIGURE 7.4 In addition to bulk cross-linked systems, the swelling of cross-linked microparticulate polymeric systems provides interesting opportunities for rheology control. As the particles swell, they first occupy a significant volume fraction of the dispersed phase and then reach a point at which all discrete swollen particles start to overlap and touch. Diameter ratios of 1:10:20, yielding a net 8000-fold volumetric swelling, is depicted.

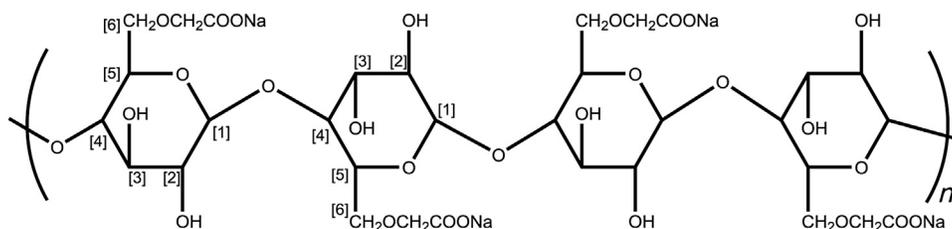


FIGURE 7.5 Representative structure of sodium carboxymethyl cellulose. For graphic convenience, only substitution at the six-position is explicitly shown. However, all three hydroxyl positions are available for substitution, and a real polymer will be comprised of a mixture of primarily unsubstituted, monosubstituted, or disubstituted monomer residues. This example is an idealized DS = 1 sodium carboxymethyl cellulose.

scale established by the dimensions of the swollen particle. In general, our attention will be restricted to linear polymers, since they comprise the majority of systems of direct interest.

7.1.2 Types of homopolymers and copolymers

In dealing with polymeric materials, cautious delineation of whether a material is a homopolymer or a more complex copolymer is an extremely critical initial step in understanding the range of properties that can emerge in everyday use. In general, most of the polymeric materials that we deal with are much more profitably handled and understood if it is explicitly recognized that they are copolymeric in reality, and the detailed sequence of the various residues is an important variable that can influence application properties in use. In some cases the distinctions are clear, while in others they are not.

As a specific example of the potentially significant impact that a sequence can have on a material, consider a simple AB copolymer that possesses equal molar amounts of A and B (Fig. 7.1). For the same average chemical composition, molecular weight, and gross architecture, a significant range of structural archetypes can be prepared by manipulating only the sequence of the monomer units. That sequence can run from

purely random to somewhat blocky, from multiblock to diblock, and to purely alternating structures. If the monomer residues possess differing solution properties, for example consider a case in which one residue is relatively hydrophobic while the other is very hydrophilic, the sequence can have an overwhelming influence on properties such as solubility, phase behavior, and packing in the solid state. As a specific case, consider poly(*co*-ethyl acrylate-methacrylic acid) (Fig. 7.1). The alternating and diblock architectures will yield vastly different physical properties (solubility, mechanical properties) and performance traits despite the equivalence of molecular weight and average composition. Naturally, the argument can be extended to include a physical mixture of the two homopolymers, which provide the same average molecular weight and composition values. Again, one has a system of near-identical molecular weight and composition, but the performance is anticipated to be distinctly different. In fact, the component polymers would likely be immiscible in the melt state and prone to segregate if deposited from the solution state in, for example, a coating application.

As a second example, consider the simple case of sodium carboxymethylcellulose with an average degree of substitution (DS) of one. In total, carboxymethyl substitution can occur at up to three hydroxyl positions on any anhydroglucose residue (Fig. 7.5).

In principle, a sodium carboxymethylcellulose chain can be comprised of unsubstituted anhydroglucose, have monosubstitution at either the two, three, or six hydroxyl positions, disubstitution at the 2/3, 2/6, or 3/6 positions, or be a fully trisubstituted monomer. Even if the added detail of positional substitution is ignored and we consider only unsubstituted, monosubstituted, disubstituted, and trisubstituted monomers as distinct entities, the system has to be considered as an ABCD copolymer. As noted, the detailed sequence distribution of the A, B, C, and D monomer residues can have an impact on the final properties of the material if the intrinsic properties of those constituent monomers (polarity, hydrophobicity/hydrophilicity, charge state, propensity to participate in interchain hydrogen bond association) differ significantly. Obviously, the solution and solid-state behavior of a neutral sugar (anhydroglucose) will be different from a trianion salt (sodium tricarboxymethyl anhydroglucose) due to the ionic charge and steric packing requirements of the latter and the facile possibility for hydrogen bond formation for the former.

As illustrated by the examples, one expectation is that microstructural sequence variations will impact the local chemical nature of subsections within a polymer chain. In the case of poly(*co*-ethyl acrylate-methacrylic acid), we see a transition from a nominally hydrophilic alternating copolymer to a system with distinct hydrophobic and hydrophilic blocks. In terms of expected solubility in water, the hydrophobic block will not find an aqueous environment amenable. Depending on the net balance of segment lengths and position along the backbone, this may manifest itself as anything from partial insolubility with a high propensity to swell, complete solubility with a tendency to adsorb onto surfaces, a tendency to self-associate in solution, or as gross insolubility in pure solvents with a decided need to employ binary solvent mixtures to achieve complete dissolution. A reality with polymeric materials is that all of these possibilities can, in principle, be expressed by materials of the same average composition via adjustment of molecular weight and chain microstructure sequence.

The case with synthetic copolymers is fairly obvious and readily understood on the basis of the respective behavior of the constituent monomers. It is a less obvious situation with derivatized cellulosics, even though the underlying issues are identical and similar trait differences for nominally similar compositions are possible, although the underlying physical phenomena are somewhat distinct. With cellulosic derivatives, aside from the cases of cellulose esters and ethyl cellulose, the possible constituent monomers are all fairly hydrophilic. However, similar issues remain and tend to be tied to the potential formation of

hydrogen bonding junction zones in structurally regular domains of the material. These structurally regular domains can be due to short runs of contiguous unsubstituted anhydroglucose or uniformly substituted contiguous run lengths. In both cases, the underlying feature is a structurally regular domain that can be annealed into a highly ordered domain for which the primary events of dissolution (solvent penetration and separation of the packed chains) are kinetically unfavorable due to cooperative multipoint hydrogen bond association.

This added level of complexity, which is intrinsic with derivatized cellulosic excipients but an important operational detail for many polymeric samples, needs to be appreciated in order to understand why materials that possess very similar average compositions can display rather diverse end use performance attributes in different applications.

7.2 BASIC CONCEPTS AND CHARACTERIZATION OF POLYMERIC MATERIALS

Some specific example polymers were described in [Section 7.1](#), as were some of the key traits used to characterize these polymers. In this section we'll delve somewhat deeper into the measurement of these traits and the interrelationships between them.

At the most basic level, a polymeric material is defined by the average molecular weight distribution and average composition. As has already been seen with molecular weight, the net range in molecular weight sampled is enormous. This can have important consequences. Traits that are dependent on properties showing variation, take molecular weight as a specific example, may display particular sensitivity to specific portions of the molecular weight distribution. What this means is that those traits that are molecular-weight dependent may differ between materials with nominally the same average molecular weights. A specific example would be the complete shear rate dependent flow curve of a blend of high and low molecular weight materials with that which is a pure intermediate molecular weight.

7.2.1 Polymer composition

At the basic level, polymers are characterized by average composition variables that reflect either the total level of secondary substitution for derivatized systems (eg, cellulose ethers) or the level of constituent monomers for a synthetic or natural copolymer system.

For example, cellulosic derivatives are compositionally characterized by the percent weight of the functional group attached to the backbone, the degree of substitution (DS) per anhydroglucose, or the total molar substitution (MS) per anhydroglucose residue. These three modes of characterization are largely interchangeable with the preferred quantity often dependent on historical legacy and whether the substituent can form an oligomeric pendant group. In the latter case, the DS would not fully characterize the net amount of substituent on a chain.

It is important to recognize that the definition of an operational functional group may include contributions from both the anhydroglucose residue and the added functional reagent, leading to apparent percentage of weight function groups that may appear inordinately high. A good example of this would be ethyl cellulose, in which the average composition is typically expressed as the percentage of ethoxyl content. In this case, the ethyl portion of the ethoxyl group is derived from the derivatizing reagent (ethyl chloride), while the oxygen atom is provided by the anhydroglucose residue. For a typical N or standard type ethylcellulose, a DS of 2.5 corresponds to a weight percentage of ethoxyl of 48.5. However, the actual percentage of mass imparted by the added ethyl group is 31.3%, with the remainder contributed by the oxygen atom that is already a part of the main backbone polymer.

The second manner to characterize the composition of cellulose is to speak of the DS. Each anhydroglucose residue along a cellulosic backbone possesses three reactive hydroxyl groups, located specifically at the C2, C3, and C6 positions. The average DS of a material quantifies the average number of hydroxyl groups that are derivatized per anhydroglucose. The maximum DS of any cellulosic material is 3, at which point all reactive hydroxyl functionality will have been consumed. The C2 and C6 positions are the most reactive sites and will generally carry the bulk of the substituents.

When the derivatization reagent effectively caps the reactive hydroxyl functionality (eg, methyl, ethyl, or carboxymethyl functionality), the amount of bound functionality quantifies both the degree of hydroxyl substitution and total MS. However, as already noted, if the substituent is able to oligomerize, as is the case with hydroxyethyl or hydroxypropyl substitution, the connection between DS and MS starts to diverge. Furthermore, in principle, the net MS provided by an oligomerizing functional group is not bound to an upper limit determined by the number of backbone reactive sites, although steric constraints and reaction efficiency do provide a pragmatic limit. Of all available cellulose derivatives, hydroxypropyl cellulose (HPC) is the most highly substituted system, with MS levels routinely in the vicinity of four.

In the case of synthetic copolymers, composition is typically determined by the average mole percent or weight percent of the various copolymer constituents, and/or the charge state for a titratable functionality. In general, this is controlled by the charge composition of the reaction mixture used to prepare the product.

In either case, there are a variety of experimental techniques that can be used to quantify the mean composition of the material. These techniques include direct functional group analysis, in the case of the derivatized cellulose derivatives, while the average monomer composition is generally the target for synthetic copolymer systems. In part, this is related to the potential complexity with cellulose derivatives that possess chain-extended pendant groups.

One significant compositional difference between polymers and low-molecular-weight materials is that the detailed sequence distribution of the constituents at equivalent average compositions can have a significant impact on the final solution and solid-state properties of the polymer.

In contrast to the situation that exists with the determination of the average material composition, there is a dearth of direct experimental techniques that provide information on the sequence of monomers in a copolymer system. In general, one is left with fairly indirect experimental probes to assess monomer sequence.

In broad strokes, these indirect probes fall into two general classifications. First, there are the techniques that degrade the polymer to an oligomeric species and then analyze the compositional heterogeneity of these oligomeric materials. While this approach provides insight into the compositional heterogeneity of the system, ascribing the difference observed between interchain and intrachain sequence variations is sometimes quite ambiguous, since one is unable to trace the fragments back to the originating polymers.

The second strategy is to examine the response of the system to the applied challenges. Specific examples would include examining the solubility behavior in a variety of pure and mixed solvent systems, characterizing solubility as a function of temperature (cloud point) or using site-directed cleavage as an approach to probe specific structural motifs. An example of the latter would be enzymatic degradation, which is selective to the presence of short runs of contiguous unsubstituted anhydroglucose. Both approaches have appeared in the literature.⁹⁻¹³

In each case, an indirect response is used to provide qualitative insight into the presence or absence of specific run sequences. The utility of this approach is that it provides insight into the origins of observable performance differences between materials that have the same average composition and molecular weight.

At this stage, the information derived from these types of measurements remains semiquantitative.

7.2.2 Molecular weight

Owing to the dispersity in chain lengths and potentially number of substituents per residue of an assembly of polymeric molecules, molecular weights must be discussed in terms of distribution averages. Three distinct types of averages are generally considered: the number, the weight, and z-average molecular weights.

Defining relationships for these three quantities are as follows:

$$M_n = \frac{\sum_i n_i M_i}{\sum_i n_i} = \frac{\sum_i w_i}{\sum_i \frac{w_i}{M_i}}$$

$$M_w = \frac{\sum_i n_i M_i^2}{\sum_i n_i M_i} = \frac{\sum_i w_i M_i}{\sum_i w_i}$$

$$M_z = \frac{\sum_i n_i M_i^3}{\sum_i n_i M_i^2} = \frac{\sum_i w_i M_i^2}{\sum_i w_i M_i}$$

with

$$w_i = n_i M_i$$

where:

w_i is the mass of the fraction of polymer chains with molecular weight M_i ;

n_i is the number of these chains.

For a perfectly monodisperse polymer sample, $M_w = M_n$. One more frequently speaks of the population polydispersity or M_w/M_n , which is equal to 1.0 for a perfectly monodisperse sample, since all the chains in that sample have precisely the same molecular weight. For the materials being discussed here, sample polydispersities will generally fall in the range of 10–20, dropping down to values of 3 or so for rather low-molecular-weight materials, and occasionally rising above 20 if the systems of differing viscosity grade have been blended. In understanding the performance of polymeric materials, high-molecular-weight polydispersity can often be a decided benefit. The most extreme example of this would be a synthetic polymer in which a residual monomer serves as an integrated plasticizer of the polymeric solid to help control mechanical properties of the system. To varying extents, most low-molecular-weight constituents

(including moisture and low-molecular-weight oligomers) can serve this type of role.

While the three molecular weight averages may appear to be a simple mathematical construct to characterize a polydisperse population, the origin of these relations resides in the different classical methods that one can employ to experimentally determine the absolute molecular weight of a polymer and the distinct averaging schemes operative in these methods. The various techniques used to measure polymer molecular weight are well described in the literature.^{14–16}

Colligative property measurements of absolute molecular weight (vapor pressure lowering, boiling point elevation, osmotic pressure) are sensitive to the number average molecular weight. Techniques such as light scattering can, under certain circumstances, yield the weight-average molecular weight. Finally, ultracentrifugation-based methods yield z-average molecular weight. In other words, the differing physical response for each of the measurement approaches provides intrinsically different forms of averaging within the polydisperse population. In addition to these absolute methods for determining molecular weight, any physical observable that possesses a molecular weight dependence, for example, solution viscosity at a fixed concentration can be used as an indirect proxy for a molecular weight determination, with operational correlation methods providing the needed link to the actual molecular weight.

In recent years, size exclusion chromatography (SEC) has largely replaced these classical approaches for routine absolute molecular weight determination. SEC has a distinct advantage over the classical measurements in that it is able to provide direct information on the complete molecular weight distribution via a direct separation based on the hydrodynamic size of the molecules in solution. There are some additional pragmatic issues that potentially improve the robustness of the SEC-based measurement including:

- Since a separation is performed, contamination of the sample with low-molecular-weight impurities has an inconsequential impact on the final result, since their contribution can be ignored at the data processing step.
- As a corollary, the sample concentration does not need to be accurately known in order to obtain a viable measurement. This can be of enormous help when dealing with in-process or formulated product samples.
- There are minimal sample requirements. Typical injected samples are 100–200 μL with a net concentration in the mg/mL range. This can be advantageous when a sample is limited (say in debugging processing details), but it can have a

negative side with respect to preparing a representative sample for analysis, as the material is very heterogeneous. Naturally, subsampling of a large parent solution can readily address this issue.

The hydrodynamic size of a chain in solution with fixed topology (ie, linear or branched) will scale with molecular weight, so the operational separation is effectively one of molecular weight and provides for estimation of the various distribution quantities. Since the common detection schemes are generally concentration sensitive, the i th weight fraction (w_i) is the experimentally determined quantity, thus M_w is based on the actual analytical measurement results. In contrast, M_n and M_z rely on derived calculations from the acquired analytical with heavy weighting at either the low- or high-molecular-weight wings of the distribution, which significantly lowers the precision of their determination. For a well-controlled and calibrated system, long-term variability of M_w determinations are generally better than $\sim 5\%$ relative with M_n , and M_z often $\sim 10\text{--}15\%$ precision. Note that these are rough results. Observed precision is composition dependent. Sample requirements, such as the need to employ a binary mobile phase to obtain a fully soluble form, can impact precision. Finally, shear forces in an analytical SEC column can be quite high. SEC system flow rates suitable for low- and moderate-molecular-weight materials (1.0 mL/minutes for typical $\sim 7\text{--}8$ mm inner diameter SEC columns) may yield in situ shear degradation of the higher-molecular-weight grade materials available. The obvious approaches of either lowering the flow rate (to 0.25–0.50 mL/minutes) or using SEC packing materials with a larger particle size will remedy this problem.

By and large, routine SEC-based molecular weight determinations generally yield molecular weight averages that refer to chemically distinct narrow molecular weight distribution calibration standards used in calibrating the chromatographic system elution volume–molecular weight relationship. As such, reported molecular weights are often referred to as relative or equivalent molecular weights. Values provided by many laboratories adhere to this methodology. Finally, while most materials mentioned (aside from sodium carboxymethyl cellulose) are nominally nonionic, it is always strongly recommended that users employ some level of dissolved indifferent electrolyte in the SEC mobile phase. The reason for this is that even nominally nonionic polymers may possess low levels of carboxylate functionality due to adventitious oxidation events during preparation or aging. In the absence of screening indifferent electrolytes, chains that possess even a low level of charge may be electrostatically

excluded from the internal pore volume of the packing material. In the absence of molecular weight-sensitive detection, this occurrence can yield incorrect molecular weights, since the elution of the sample is now influenced by factors outside of size alone.

More recently, SEC separations have been combined with molecular weight-sensitive detection schemes (online light scattering, online viscometry) to enable integrated development of operational absolute molecular weight–elution volume calibration of the system and online determination of absolute molecular weight information. The potential compositional complexity of the copolymeric systems used as pharmaceutical excipients renders light scattering determinations of molecular weight rather more complex than simple characterization of typical synthetic homopolymer systems. While the absolute nature of light scattering molecular weight determinations are often touted, that ideal is often not completely realized with the complex copolymeric systems discussed here. Furthermore, absolute molecular weight determinations are quite dependent upon the determination of an accurate, specific refractive index increment (dn/dc). Inspection of the literature for tabulated values of this quantity often shows a wide range of values in rather similar solvent systems. Ultimately, the accuracy of absolute molecular weights often relies on the quality of this secondary quantity. Under well-controlled conditions using purified samples, dn/dc can be determined with high precision. The usual secondary issue associated with this is how strongly dn/dc varies with composition and to what extent composition of the samples also varies.

While productive use of molecular weight-sensitive detection relies on judicious understanding of all the factors required to generate quality data, one overriding value of the approach is that if adsorption of the analyte occurs on the stationary phase packing material, the result is unaffected to the degree that elution zones may overlap with genuinely low-molecular-weight material. In routine SEC, which relies on the use of a secondary calibrant to allow creation of a MW/elution volume calibration curve, there is no direct indication if analyte is adsorbing to the stationary phase, and this will naturally have an enormous impact on any calculated results.

Although SEC is certainly one of the most used approaches to polymer molecular weight determination, the batch classical methods are still used.

Colligative property measurements include both vapor pressure and membrane osmometry. While both measurements rely on colligative effects, in a practical sense, they complement one another rather well.

Owing to the physical limitations of membranes, membrane osmometry is ill suited for relatively

low-molecular-weight polymers ($M_n < 25,000$ Da), and finds its main utility with relatively high-molecular-weight materials and, under carefully controlled conditions, polyelectrolytes. Since low-molecular-weight contaminants are able to equilibrate across the membrane, membrane osmometry is insensitive to low-molecular-weight contaminants. It is also insensitive to chemical heterogeneity, which is a major advantage in the analysis of copolymeric materials.

In contrast, vapor pressure osmometry tends to excel in the lower-molecular-weight region ($M_n < 20,000$ Da), for which membrane osmometry is ill suited. However, the technique is very sensitive to the presence of any low-molecular-weight impurities, which requires the use of highly purified samples and is inapplicable to polyelectrolyte systems.

Although colligative property measurements have a well-founded physical basis, any methodology that allows an experimentalist to count molecules in an assembly can be used to provide an estimate of M_n . Other techniques that have seen utility in the literature include end group analysis, in which unique functionality or reactivity or end groups are used as a mechanism to count the total population of chains in a sample.

At the other end of the spectrum, analytical ultracentrifugation can be used to quantify the M_z of a sample population. While this technique has seen substantial use in the analysis of proteins and other biologically derived polymers and has had a recent resurgence with the commercial rerelease of the Beckman Coulter Optima XL-A series of instruments, it remains something of a niche technology despite the appreciable technical benefits (lack of a potentially adsorptive stationary phase as in SEC, wide range of solution conditions possible, ability to assess complicated equilibria, and ability to handle ultrahigh molecular weight and colloidal systems under conditions of very low sample shear).

The measurements of M_w averages tend to dominate molecular weight characterization of polymers. For the sake of this discussion, we will consider methods that directly measure M_w together with methods such as viscometry, which yield a response that generally tracks M_w .

For the determination of an absolute M_w , light scattering, either alone or in conjunction with SEC, is the primary experimental approach. The use of SEC with either narrow distribution molecular weight standards or inline viscometric detection with universal calibration transformation, provides results that can range from a simple relative molecular weight, if the calibration standards are chemically distinct from the analyte, to near absolute M_w results.

Potential pitfalls of light scattering include the possible impact of dust or suspended precipitates for

batch-style measurements, association phenomena that result in the inflation of the experimental results, the use of binary solvents to improve polymer solubility or the lack of strict adherence to constraints required to guarantee that absolute results are obtained (chemical homogeneity of the chain populations, maintaining constant chemical potential of counterions for polyelectrolyte samples (often approximated by the use of "swamping" electrolyte in large relative excess), accurate values of dn/dc).

Pairing light scattering with a prior SEC separation adds substantial power to both techniques. While SEC provides a means to separate material according to its hydrodynamic volume in solution, it also provides an excellent means to filter the analytical sample to eliminate dust and other artifacts from the light scattering signal.

While the underlying fundamental physical quantity of interest is the molecular weight of a material, and most performance traits are related to the molecular weight, most materials are classified in a more operational manner via grade classification according to a viscosity measurement under specified conditions. Naturally, viscometry or rheology can be used as a method to quantify polymer molecular weight, as well as to provide other insights into the nature of the material.

7.2.3 Rheological properties

Rheology is the study of the deformation and flow of a material when subjected to an applied force. The practical consequences of rheology play out in everyday experiences: in the kitchen as one thickens a water-based fluid with starch or forms a jelly through the use of gelatin dissolved at high temperature. In both extremes, the mechanical properties of the final preparation are manipulated through the judicious addition of a polymeric material. The science of rheology attempts to quantify the material changes exemplified by these systems. Detailed treatments of the complete scope of rheology are readily available.^{17–20} Dealy has also prepared a convenient summary of official nomenclature and basic terms related to rheological science.²¹

In assessing the response of a material to an applied force, it is critical to appreciate that the applied force can span many orders of magnitude, ranging from simple gravity acting upon a particle suspended in a fluid medium to the very high shear rates experienced in high-speed mixing or high deformation rates experienced in high-speed conveyance and manufacture of solid products. Depending upon the particular details in manufacture and of usage, this entire range of shear

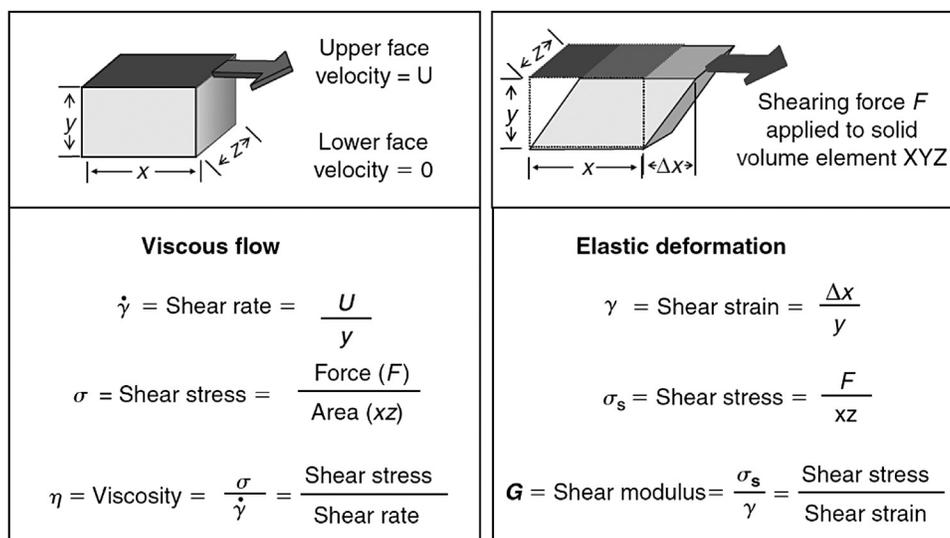


FIGURE 7.6 The basic mechanics of the flow of viscous liquids and deformation of elastic solids. In viscous flow, the energy input into the system is dissipated, while it is stored in the pure elastic deformation of a solid. Real materials are viscoelastic in nature, displaying both viscous and elastic character, with the balance determined by both the magnitude and duration of the applied force.

or deformation rates may be sampled at various points in routine usage.

Rheology considers not only the viscous flow of liquids but the elastic and plastic deformation of solids. In terms of the essential mechanics, the physical situations are quite similar (see Fig. 7.6). Real materials possess both elastic and viscous traits, with the key feature being the timescale over which the shear force is applied relative to the intrinsic relaxation time for the material.

In most cases, the response of a system is quantified by measuring the shear stress (σ , Pa) that develops in a system under the conditions of a controlled and specified shear rate ($\dot{\gamma}$, second^{-1}) for viscous flow or shear strain (γ) for pure elastic deformation. Typically, one speaks of the viscosity (η) of a fluid, which is simply the ratio of the shear stress divided by the shear rate:

$$\eta = \frac{\sigma}{\dot{\gamma}}$$

or the shear modulus (G):

$$G = \frac{\sigma}{\gamma}$$

in the case of solids.

If we restrict our attention to liquid systems for the moment, in the simplest case, which experimentally applies to simple, low-molecular-weight, nonassociating liquids, flow is directly proportional to the applied force. Equivalently, the ratio of the shear stress to applied the shear rate is a constant independent of the applied shear rate (see Fig. 7.7). Systems that behave in this fashion are termed Newtonian. Although it is not

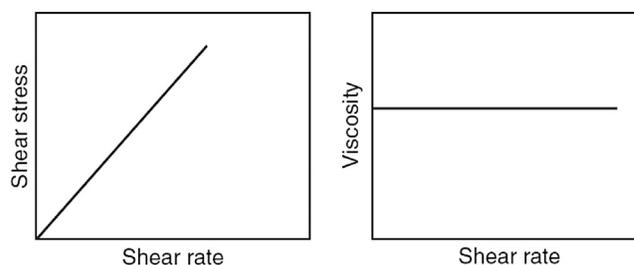


FIGURE 7.7 The simplest case for fluid flow is provided by a simple Newtonian liquid. In this case, the fluid viscosity is independent of the applied shear rate. Common low-molecular-weight unassociated liquids and solutions are Newtonian.

explicitly noted, Newtonian fluids will also display a time invariant viscosity. If the shear rate is maintained constant over time, the temperature is maintained constant, and chemical degradation of the sample does not occur, the shear stress that results, and hence the measured viscosity, is also constant. Although most common Newtonian liquids are also low viscosity, these two traits are not inexorably tied together. For example, concentrated sucrose solutions possess substantial viscosity and also exhibit Newtonian flow.

When a polymer is dissolved in a low-molecular-weight Newtonian solvent, the rheological response can become decidedly more complex. The most significant effect is that one observes that the solution viscosity is no longer independent of the applied shear rate under all conditions. One will generally observe that at vanishingly small shear rates, there will be a limited low-shear Newtonian plateau over which the solution viscosity appears independent of the applied

shear rate. As the applied shear rate is increased, one will enter a shear-thinning regime in which the apparent viscosity drops as the shear rate is increased (see Fig. 7.8). Finally, at very high shear rates, one may observe the reestablishment of a regime in which the apparent viscosity is again independent of the applied shear rate, yielding a limited high-shear Newtonian plateau.

An example with actual data is provided in Fig. 7.9. This profile shows the shear-thinning behavior of various viscosity grades of 2.0 wt.% hypromellose in water. Note that even at rather low effective shear rates, achievement of a well-defined low-shear Newtonian plateau is not assured. Finally, the fairly strong shear rate dependence

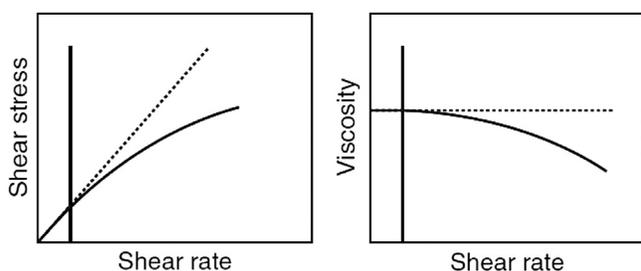


FIGURE 7.8 Most solutions of polymers exhibit some degree of non-Newtonian flow behavior. Simple shear thinning is the most straightforward case. In this example, the system is Newtonian until a critical shear rate is achieved. Above this critical shear rate, the apparent viscosity drops with further increases in shear rate.

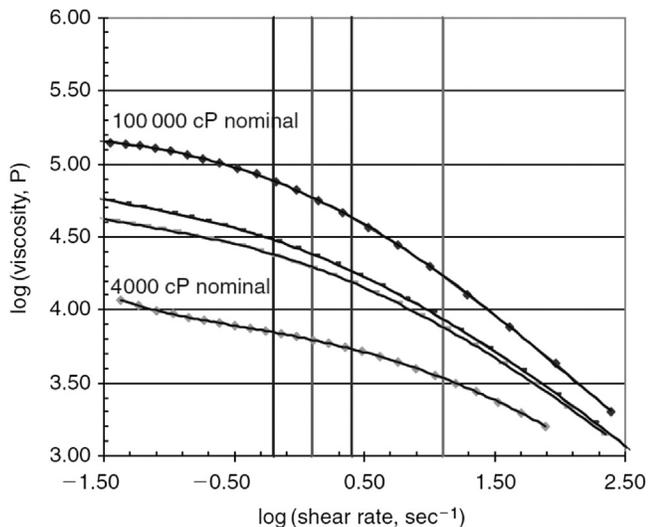


FIGURE 7.9 Typical shear-thinning behavior exhibited by 2 wt.% hypromellose solution in water. The minor apparent upturn in the apparent viscosity of the 4000 cP nominal viscosity sample is an instrumental artifact due to a low analytical signal. The vertical lines indicate (left to right) the effective shear rate applied in a Brookfield rotational viscometer equipped with a cylindrical fixture at 3, 6, 12, and 60 revolutions per minute (rpm).

in the measured viscosity of a polymeric solution can have very practical consequences. As can be observed from the estimated shear rates for a determination of viscosity using a simple Brookfield rotational viscometer under rotational speeds commonly employed in laboratory work (3, 6, 12, and 60 rpm), for a shear-thinning fluid, precise adherence to specified conditions is a clear requirement if the direct comparison of results is desired. For example, the apparent viscosity of the 100,000 cP (grade designation based on 2% Ubbelohde viscosity using the USP methodology) would appear to be roughly 75,000 cP if measured at with a cylindrical spindle at 3 rpm, while the apparent viscosity is less than 20,000 cP if measured at 60 rpm. This is the reason that the shear rate of the measurement needs to be known in assessing viscometric results, particularly when the sample is in the semidilute regime. Furthermore, while factors such as spindle rotation rates obviously impact the shear rate applied to a system, less obvious factors such as vessel size (if small relative to the rotational fixture in a Brookfield viscosity measurement) can also contribute to the actual shear rate applied to the sample.

In addition to the pronounced shear rate dependence in the apparent viscosity, the concentration dependence can be broken into two regimes for nonelectrolyte polymers, with some added complexities apparent in the case of polyelectrolytes. If one views the state of a discrete polymer chain as the concentration of a system is increased, the solvated chain will rotationally sweep out a distinct and large volume element of the solvent. In a dilute solution, on average, all of the chains will be able to rotationally average their motions without any hindrance from neighboring polymer chains. However, as the concentration is increased, one will reach a point at which the rotationally averaged volume elements first touch, then overlap. Once these volume elements start to overlap, the chains start to entangle with one another. When this occurs, the concentration dependence of the apparent viscosity at constant shear rate increases substantially. This regime, under which polymer chains overlap and entangle with one another, is referred to as the semidilute concentration regime. If one were to examine the profile of apparent viscosity against concentration in log–log coordinates, two distinct power law regimes are generally apparent in the dilute and semidilute regimes. Power law exponents are generally close to 1 in the dilute regime and increase to 3–4 as one transitions to the semidilute regime (see Fig. 7.10). From a fundamental basis, characterization of the apparent viscosity dilute and semidilute regimes is best done using results extrapolated to zero shear rate (ie, reflective of the low-shear Newtonian plateau). However, operationally, these analyses and general guides also apply with reasonable fidelity under

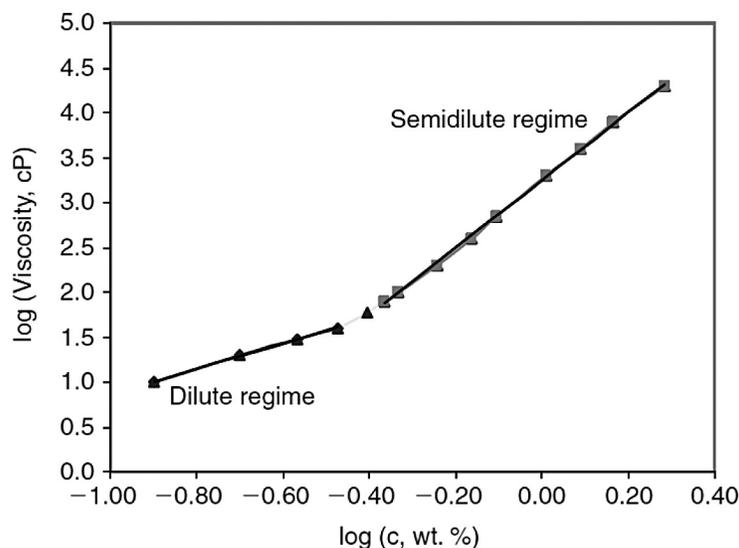


FIGURE 7.10 Example of the concentration dependence of viscosity for sodium carboxymethyl cellulose (DS ~ 0.7 , 7H type) as concentration is varied from roughly 0.10 to 2.0 wt.%. Clear distinction of the dilute and semidilute regimes is apparent. The solutions represented in this example were prepared using pure water as the solvent, hence the ionic strength of the solution is not held constant as the polymer concentration is increased. This results in a slight lowering of the power law slope in both the dilute and semidilute regimes.

conditions of finite shear. The distinction is important, since most workers will have access to a Brookfield rotational viscometer to characterize these materials, with this style of measurement generally being practiced at effective shear rates well above that needed to observe the low-shear Newtonian plateau.

In the case of polyelectrolyte, additional complications exist due to the strong dependence of the expansion of a solvated chain on the net ionic strength of a solution. Fig. 7.11 depicts the dependence of the intrinsic viscosity of a sodium carboxymethyl cellulose sample as a function of ionic strength in dilute solution. As one would anticipate, the addition of an indifferent electrolyte screens the repulsion of like charges along a polyelectrolyte backbone, allowing the chain to adopt a more relaxed random coil configuration in solution. The net result is a drop in viscosity in the system. As depicted in Fig. 7.11, the drop in viscosity can be relatively large for modest changes in ionic strength.

In a solution with no added indifferent electrolyte, the general viscosity behavior of polyelectrolytes is similar to nonelectrolytes, with the added feature of the progressively increasing screening of bound charge sites yielding an apparent lowering of power law exponents in both the dilute and semidilute regimes, since the apparent ionic strength increases with polymer concentration. This complexity can be suppressed by the addition of an indifferent electrolyte to maintain a nearly constant net ionic strength in solution. Naturally, this can further suppress viscosity build in the system.

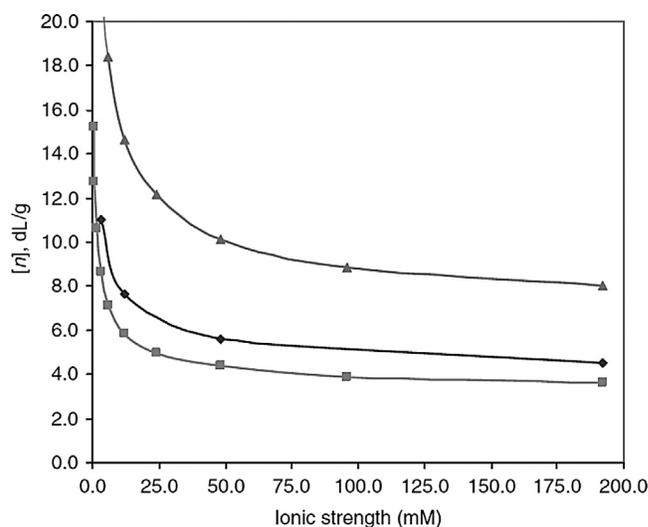


FIGURE 7.11 Impact of an added electrolyte on the intrinsic viscosity of a typical polyelectrolyte, in this case sodium carboxymethyl cellulose (NaCMC). (Original data from Pals, D. T. & Hermans, J. J. (1952). *Rec. Trav. Chim. Pays-Bas*, 71, 433–443.) At low ionic strength, the NaCMC chains adopt a relatively rigid, rod-like conformation due to electrostatic repulsion between adjacent chain-bound anionic charges. As the ionic strength is increased, this repulsive interaction is screened, and the polymer adopts a less rigid conformation.

Finally, in addition to solution shear thinning due to alignment of chains by the applied shear field, the presence of labile association aggregates can yield a time-dependent apparent viscosity that is dependent on the recent shear history of the sample (see Fig. 7.12). This characteristic is termed “thixotropy,” and it arises

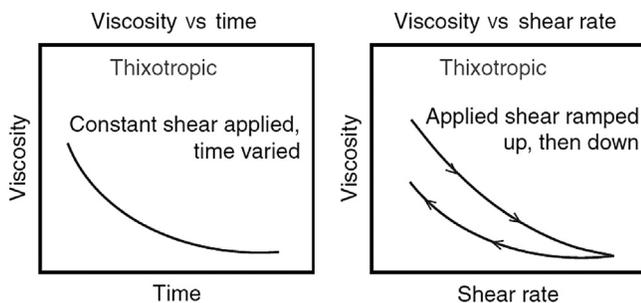


FIGURE 7.12 Polymeric systems in which reversible interpolymer association is possible display a characteristic known as thixotropy. Basically, the mechanical stress applied to the system causes reversible disassembly of the aggregate network. Under conditions of steady shear, this yields a slow decrease in the apparent viscosity over time. The extent of disassembly is dependent on the net force applied to the system, hence the drop in viscosity can occur from either a quiescent state or if a sheared system is subjected to a higher shear rate. By the same token, on a decrease in applied shear rate, the apparent viscosity exhibits recovery. The magnitude of the effect is generally quantified by measuring the disparity in flow curves obtained in a simple experiment in which the shear rate is ramped up then down with continuous recording of the viscosity.

from the association-dissociation of aggregates, which is much slower than the timescale of the measuring experiment.

Although relating solution rheology to molecular weight is best pursued using extrapolated zero shear values, the use of power law relationships in the semidilute concentration regime at finite shear typically yields operationally useful relationships for the quick estimation of molecular weight. Owing to pragmatic instrumental limitations, these experiments generally involve data acquired over a range of shear rates. This can lower the overall quality of the correlation, but it is still useful for routine estimates.

Power law relationships of the form:

$$\log(M_w) = a + b * \log \left[\frac{\eta}{c^\alpha} \right]$$

are often found to operationally model the data. In the equation above, M_w is the average molecular weight, while η is the solution viscosity at concentration c . The constants a , b , and α can be viewed simply as mathematical fitting constants, although α is related to the power law concentration exponent in the semidilute regime. An example of this treatment is shown in Fig. 7.13 for three types of cellulosic derivative. The specific relationships shown are as follows:

HPC:

$$\log(M_w) = 5.08 + 0.305 * \log \left[\frac{\eta}{c^{3.2}} \right]$$

Hydroxyethyl cellulose:

$$\log(M_w) = 5.00 + 0.306 * \log \left[\frac{\eta}{c^{3.1}} \right]$$

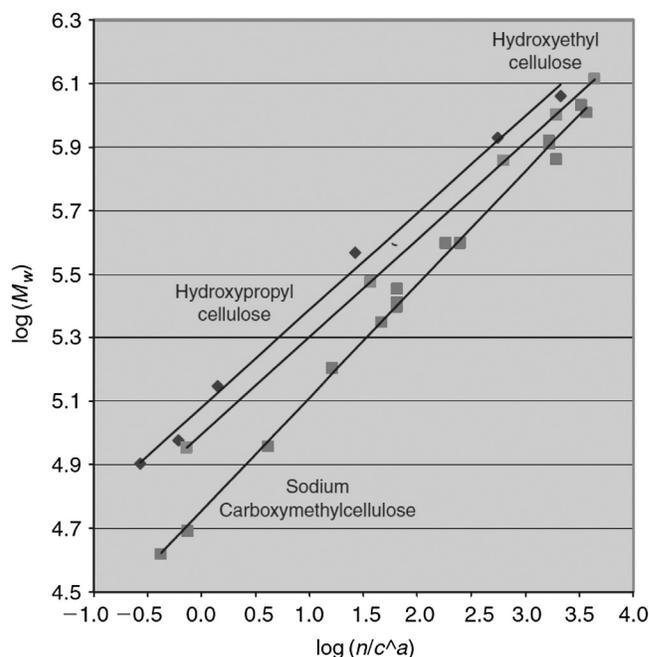


FIGURE 7.13 Polymer master viscosity/concentration/ M_w profiles for cellulose ether excipients using Brookfield viscosity values at variable concentration and assuming a simple power law relationship. Separate curves for HPC, hydroxyethyl cellulose, and sodium carboxymethyl cellulose are shown. These curves span the entire product range viscosity for the derivative types shown and listed in Table 7.8, later in this chapter.

Sodium carboxymethyl cellulose:

$$\log(M_w) = 4.78 + 0.356 * \log \left[\frac{\eta}{c^{3.1}} \right]$$

where:

M_w is the nominal material molecular weight;
 η is the solution Brookfield viscosity;
 c is weight percentage polymer concentration.

Naturally, these relations can be rearranged to yield initial estimates of the concentration of any specific grade of polymer required to achieve a target of viscosity.

There are a few key points related to rheology and polymers that are worth noting:

1. Since the rheology of a polymer solution is molecular-weight dependent, rheology/viscometry can be used as an indirect proxy to monitor molecular weight.
2. Although, strictly speaking, one should use the apparent viscosity extrapolated to zero shear in modeling the molecular-weight dependence of polymer solution viscosity, reasonably good master curves obtained at finite shear rates and at variable concentration can be used to provide decent pragmatic estimates of the molecular weight of a polymer sample.

3. Owing to the very strong concentration dependence, the actual polymer concentration needs to be accurately known. Since the power law exponent of viscosity–concentration curves in the semidilute region have a log–log slope of 3–4, an $x\%$ error in specifying the concentration yields a $3x\%$ – $4x\%$ error in the calculated viscosity.
4. Solution viscometric experiments generally provide information related to the average M_w of a system. No information on the breadth of the molecular weight distribution is provided.
5. The magnitude of the exponent in the power law dependence in viscosity as a function of concentration, as seen in Figs. 7.10 and 7.13, is the origin of typical rules of thumb used to estimate viscosity at different concentrations. For example, a doubling in weight percentage concentration often yields an increase in viscosity of roughly 10-fold, which follows directly from the type of power law behavior shown in Fig. 7.10.

7.2.4 Polymers in solution

Understanding the unique solution behavior of polymers mainly resides primarily in appreciating a few key points.

First, the high molecular weight of a polymeric solute significantly lowers the entropy of mixing for a polymer solvent binary system, lowering this component of the net free energy of solution. This was treated some time ago by Flory⁶ and more recently by Sanchez and Lacombe,^{22–24} which captures the essential results.

At an ideal level, taking a solution as a simple lattice model, we find:

$$\Delta S_{\text{mix}} = -R(n_1 \ln(\varphi_1) + n_2 \ln(\varphi_2))$$

or

$$\Delta S_{\text{mix}} = -R \left[\frac{\varphi_1}{DP_1} \ln(\varphi_1) + \frac{\varphi_2}{DP_2} \ln(\varphi_2) \right]$$

As is apparent from the inverse dependence of the prelogarithmic factor of each term on the degree of polymerization (DP) or, equivalently, the molecular weight of the components in the mixture, if either one or both of these components is a high-molecular-weight material, the magnitude of the entropy is lowered as the molecular weight is increased. In broad strokes, as the molecular weight increases, the free energy driving force for dissolution is lowered, since the gain in entropy by the polymer on dissolution is quite low.

One direct consequence of the lowered entropy of solution is that in a chemically homogeneous

system precipitation of a polymeric solute, as solvent conditions transition from good to poor, it starts with the high-molecular-weight portion of the distribution and proceeds with decreasing molecular weight. This provides a relatively facile manner to perform crude molecular weight-based preparative isolation. It also suggests that for a partially soluble material (again, assumed to be chemically homogeneous), the undissolved fraction is typically enriched in the high-molecular-weight fraction.

Secondly, most polymers under consideration here are copolymeric materials, for which the various component monomers have rather different intrinsic solubility. For example, in the case of HPC, a single unsubstituted anhydroglucose moiety is quite hydrophilic, while a heavily hydroxypropylated anhydroglucose residue is rather hydrophobic. The constituent monomers in a real sample will span a wide range in hydrophobic nature, thus their distinct distribution across chains (interchain heterogeneity), and within chains (intrachain heterogeneity). The net result is that at any specific solvent composition a situation can arise in which subpopulations of entire chains may be soluble or insoluble, or discrete subsections of single chains may be solvated or unsolvated.

Thirdly, the linear array of monomer groups provides a spatial template upon which relatively low-energy intermolecular forces can operate in a cooperative fashion to yield fairly strong interchain associations. A specific example of this would be the interchain association of unsubstituted anhydroglucose runs in sodium carboxymethyl cellulose to yield textured solutions and thixotropic rheology.

With respect to gross solution behavior, the same basic rules that guide the dissolution of low-molecular-weight species also apply to polymers. As with low-molecular-weight materials, “like dissolves like.” This is captured somewhat more quantitatively in the extended solubility parameter approach,^{25–27} in which the cohesive energy of a material is divided into contributions arising from distinct types of intermolecular interactions (dispersive, polar, hydrogen bonding). While the usual admonishment that “like dissolves like” is somewhat more quantitatively expressed within the solubility parameter approach as a matching of the cohesive energy densities of the two materials (solubility is maximized when the cohesive energy densities of the solvent and solute are equal and decreases as they become increasingly disparate), the categorization of the extended solubility parameter approach places a rationale around the basic picture in terms of discrete interaction mechanisms that exist between molecules.

Unlike the situation with low-molecular-weight liquids, one cannot experimentally determine the molar

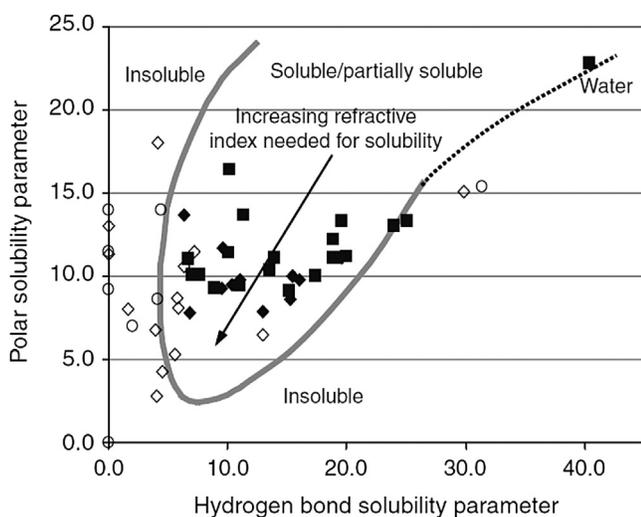


FIGURE 7.14 Solubility characteristics of hydroxypropyl cellulose as a function of polar and hydrogen bond solubility parameters. In this solubility map, the solid curve is the soluble/insoluble phase boundary presented in reference.²⁸ The dashed line is an interpolated boundary taking into account water solubility characteristics.^{27–29} Points shown represent the specific solvents listed in references^{27–29} as yielding solutions, described as clear and smooth/soluble (■), moderately granular and/or hazy/partially soluble (◆) or insoluble (○), or uncharacterized systems of unknown solubility (◇).

energy of vaporization of polymers and using the molar volume calculate a direct cohesive energy density ($\delta = (E_{\text{vap}}/V)^{0.5}$). However, one can perform challenge–response experiments to assess the solubility behavior of a polymer in a number of low molecular weight liquids (insoluble, partially soluble/swellable, soluble) and use those observations to construct solubility parameter-based maps, which can aid in the selection of optimum solvent systems for dissolving a polymeric material. As a specific example, consider HPC.^{28,29} Fig. 7.14 contains the qualitative solution behavior of HPC in a variety of solvents presented as a two-dimensional solubility map in terms of the polar and hydrogen bond solubility parameters. As is apparent, there is a reasonably clear demarcation between the insoluble and partially or completely soluble regions. Note that the partially soluble and soluble regions exhibit a substantial overlap. This is largely a consequence of the two-dimensional nature of the plot, which neglects the explicit contribution of dispersive interactions to solubility. The specific solvents for which HPC exhibits good solubility at low polar and/or hydrogen bond solubility parameters tend to be high refractive index liquids (aromatic or halogenated), which increases the dispersive contribution of the net solution energy.

The dissolution characteristics of the polymeric species become complicated when the constituent monomers have vastly different solvation requirements.

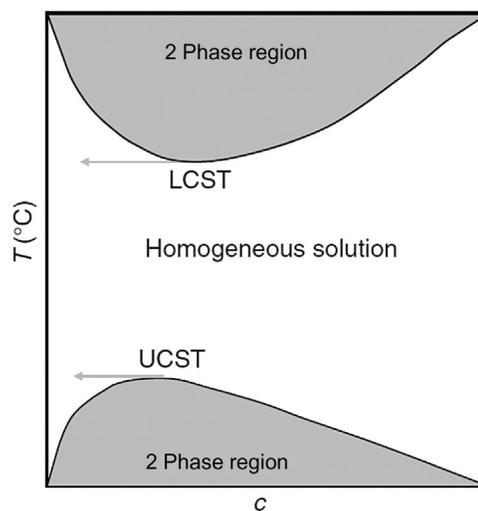


FIGURE 7.15 Schematic representation of upper and lower critical solution temperatures, UCST and LCST respectively. A UCST exists when a polymer transitions from partially soluble to soluble as temperature is raised, while an LCST occurs when a single homogeneous phase splits into two phases with the same increase in temperature. An LCST is often seen with relatively hydrophobic materials, while UCST behavior tends to be observed with systems involved in specific self-association phenomena.

In that case, the usual recommendation of “like dissolves like” may only apply to a portion of a given polymer chain. In this case, the use of binary and/or ternary solvent mixtures can often yield solutions not possible from any of the pure solvent components.

One other aspect of polymer solubility is the existence of upper and lower critical solution temperatures, referred to as UCST and LCST, respectively, seen in aqueous solutions of many of these polymers. The situation is diagrammatically shown in Fig. 7.15. In the case of an LCST, the system splits into a two-phase system comprised of polymer-rich and polymer-lean compositions at high temperature. As the temperature is lowered, the composition of these two phases approaches one another and then merges into a single phase at the LCST. Similar behavior occurs with the UCST, except that the transition from a two-phase to a one-phase system occurs as the temperature is raised.

In the current application settings, one typically observes an LCST from the perspective of a cloud point, which is simply due to performing the experiment in reverse—starting with a homogeneous solution in the single-phase region and raising the temperature until the solution splits into two phases. This occurs uniformly throughout the volume of solution, which typically yields small droplets of the polymer-rich phase dispersed in the polymer-lean phase. This generates a high level of scattered light, rendering the fluid opaque, and is the origin of the term “cloud point.”

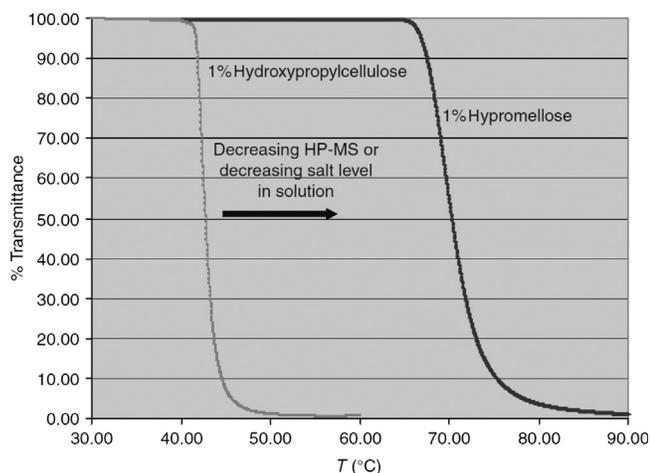


FIGURE 7.16 Cloud point curves for typical high-viscosity grades of hydroxypropyl cellulose and hypromellose (hydroxypropylmethyl cellulose). The major difference in cloud points between these two materials is reflective of the differing hydrophobicities (determined by a combination of hydroxypropyl and methoxyl groups for hypromellose). In addition to the native polymer composition, addition of an indifferent electrolyte can lower the cloud point by a few degrees for typical physiologically relevant ionic strength.

Fig. 7.16 provides an example of two chemically similar systems, HPC and hypromellose, both as 1% solutions in water. The substantial difference in cloud points is related to the substantially different hydrophobicity of these two materials. As is typical for marginally soluble hydrophobic materials, the addition of an electrolyte will move the cloud point to a lower temperature, as would an increase in the hydroxypropyl content of either system or the methoxyl level of the hypromellose sample.

7.2.5 Polymer morphology and physical properties

Polymers may consist of both crystalline and amorphous regions; the degree of crystallinity is usually expressed in terms of a weight fraction or volume fraction of the crystalline portion. The crystallinity of polymers is characterized by their degree of crystallinity and, in principle, can range from zero for a completely noncrystalline or amorphous polymer to one for a theoretical completely crystalline polymer; however, it typically ranges from 10% to 80% in real polymers.³⁰ Therefore, such crystalline polymers are often called semicrystalline. The properties of semicrystalline polymers are determined by the degree of crystallinity and by the size and orientation of the polymer chains. Polymers containing microcrystalline regions (ie, semicrystalline polymers) are generally tougher (can be bent more without breaking) and more impact-resistant than totally amorphous polymers.

The term melting point, when applied to crystalline polymers, suggests a transition from a crystalline or semicrystalline phase to an amorphous melt phase. Although abbreviated as simply T_m , it may be more properly called the crystalline melting temperature. Among synthetic polymers, crystalline melting is only associated with linear thermoplastic polymers, as highly cross-linked thermosetting polymers will decompose at high temperatures rather than melt.

In an amorphous state, the arrangement of the polymer chains is completely random. There is no restriction to chain movement from the lattice ordering of partially crystalline polymers. Therefore, amorphous polymers do not have sharp melt points; instead they soften gradually with increasing temperature. The physical properties of amorphous polymers are related to the extent of their molecular mobility in the material, which is governed by the chain flexibility and the temperature of the system.

On cooling, rubbery materials undergo a liquid-glass transition, which has also been called a rubber-glass transition. The temperature at which this transition occurs is termed the glass transition temperature (T_g), which describes the temperature at which amorphous polymers undergo a second-order phase transition from a rubbery, viscous amorphous solid to a brittle, glassy amorphous solid. Drastic changes in the physical properties, such as hardness and elasticity, can be observed during this transition as it reflects the onset of changes in the cooperative thermal motion of the polymer backbone segments. These changes are completely reversible, since the transition is a function of molecular mobility rather than polymer structure. At temperatures above T_g , the polymer chains are in relatively rapid thermal motion. The chain movement becomes progressively slower as the temperature is lowered. At T_g , the polymer chains are essentially locked in the conformation they possessed before reaching T_g . Below T_g , the polymer is virtually frozen in a glassy state with a completely random structure. The T_g of a polymer depends largely on the chemical structure of the polymer chain. The glass transition temperature may be modified by altering the chain flexibility, monomer structure and copolymer composition, degree of branching or cross-linking in the polymer, or by the addition of plasticizers. Long-chain branches may increase polymer strength, toughness, and the T_g due to an increase in the number of entanglements per chain. Increasing chain length tends to decrease the chain mobility and increase the glass transition temperature (T_g). This is a result of an increase in polymer chain interactions such as van der Waals attractions and entanglements associated with increased chain length. These interactions tend to immobilize individual chains more strongly in situ,

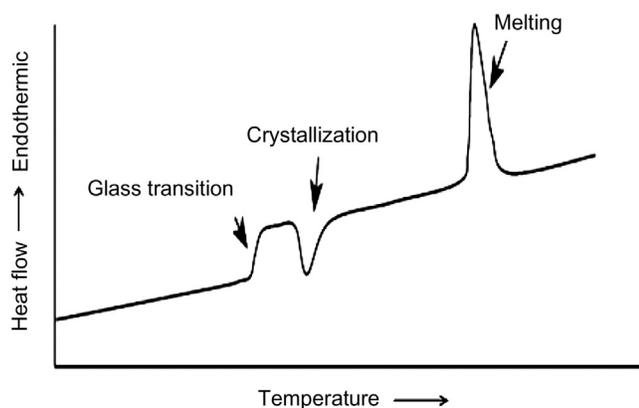


FIGURE 7.17 Typical differential scanning calorimetry (DSC) scan.

resulting in better resistance to deformation and matrix breakup, both at higher stresses and higher temperatures.

The glass temperature of a polymer can be characterized experimentally by measuring basic thermodynamic, physical, mechanical, or electrical properties as a function of temperature. Thermal method such as differential scanning calorimetry (DSC) is used routinely for this purpose. A typical DSC scan is shown in Fig. 7.17 where the heat flow is plotted against the average temperature. In addition to sharp peaks corresponding to crystallization and melting events, the change of slope of this scan occurs at the glass transition temperature, which can be related to the enthalpy change associated with this transition.

7.2.6 Structure–property relationships

In polymer chemistry and materials engineering, it is common to design novel materials and formulated systems with improved functional properties based on detailed study and understanding of how the structure of a material impacts the physical and chemical properties that are critical to the end use. In the pharmaceutical industry, it is common to apply this type of approach to the design of drug molecules. For example, quantitative structure–activity relationships are studied to enable the design of drug molecules with optimal therapeutic efficacy. A further example is the optimization of drug solubility and stability through the selection of appropriate salt and crystal forms. Similarly, a good appreciation of structure–property and structure–function relationships is also essential if formulators are to make rational, science-based choices when selecting polymers and other excipients as formulation components. Structure–property and structure–function relationships can be defined as understanding how the chemical or molecular structure of a polymeric excipient impacts the physical and chemical properties

that are critical to the end use functionality. These concepts are gaining increasing significance in the context of quality by design (QbD). QbD is defined as a systematic, scientific, risk-based, and holistic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control. A requirement of QbD is to identify critical material attributes (CMAs), which are defined as the physical, chemical, and biological properties of an input material that should be within specific limits to ensure desired quality. For polymeric excipients, this essentially requires the understanding of structure–function and structure–property relationships.

The following section will attempt to illustrate some of the major, generally applicable structure–property relationships that are of practical use and specifically relevant to pharmaceutical polymers and their use in solid oral controlled-release dosage forms. These include the impact of MW, substitution, and copolymerization on solution, gel, mechanical, and thermal properties. While the general principles are applicable across a wide range of polymers, many of the examples given here will focus on cellulose derivatives and vinylpyrrolidone polymers, as these are the most commonly used classes of polymers in oral solid dosage form design.

7.2.6.1 Molecular weight effects

7.2.6.1.1 Effect of molecular weight on solution viscosity

Many polymer properties are molecular-weight dependent, including solution and melt viscosity, glass transition temperatures, mechanical properties, and gel strength. Perhaps the most important and frequently applied structure–property relationship is the correlation between dilute solution viscosity and molecular weight. As a longer polymer chain gyrates in solution, it can be visualized to occupy a larger volume of the solvent, collide, and overlap more frequently with other long polymer chains as compared to shorter polymer chains. The initial fundamental observation and prediction that solution viscosity is proportional to polymer molecular weight was made by Staudinger and Heuer.³¹ For linear polymers, the Mark–Houwink equation provides an empirical model for this relationship:

$$\eta = kM^a$$

where:

- η is the specific viscosity;
- M is the weight-average molecular weight;
- K and a are polymer, solvent, and temperature dependent.

Generally, a varies between 0.5 and 1. For poor solvents in which the polymer remains coiled, $a = 0.5$. For good solvents, a varies between 0.65 and 0.8. For stiff, asymmetrical molecules in good solvents, a may approach 1. It should be noted this specifically applies to linear polymer molecules. Highly branched, bush-shaped polymer structures may have a large molecular weight but occupy proportionally smaller volumes in their solvated state.

7.2.6.1.2 Effect of molecular weight on mechanical and thermoplastic properties

Many physical properties of amorphous polymers, including mechanical and thermoplastic properties, show strong molecular-weight dependence. Frequently, a general relationship applies where molecular weight changes in the lower middle molecular weight range result in large changes in the physical property of interest. However, as shown in Fig. 7.18, after reaching a threshold level in molecular weight, further molecular weight increases result in only minor changes in the physical property of interest.

Often these phenomena can be explained on the basis of chain end concentration, that is, lower-molecular-weight polymer chains are shorter, and thus for the same amount of material, there is a proportionate increase in the number of molecules and thus chain ends. The chain ends tend to be associated with a greater degree of mobility and free volume as compared to the middle segments of a polymer chain. Consequently, lower molecular weight is generally associated with greater plasticity and lower glass transition temperatures. In contrast, longer polymer chains (lower chain end concentration) are generally associated with increased elasticity and flexibility.

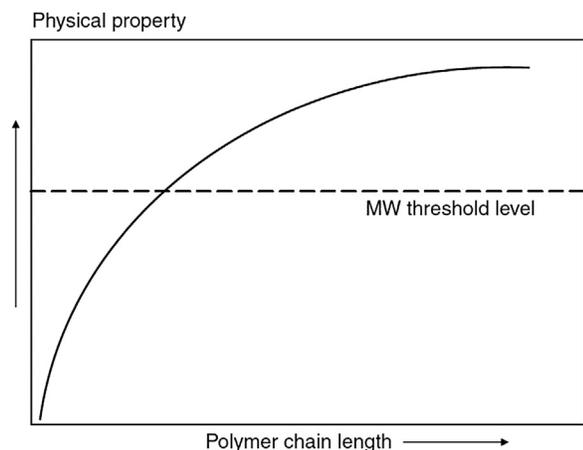


FIGURE 7.18 General relationship between polymer chain length (molecular weight) and physical properties such as tensile strength and T_g .

7.2.6.1.3 Mechanical strength of films

One of the most useful mechanical tests for polymeric and pharmaceutical materials in general is to determine its tensile strength and the accompanying stress–strain curve. This is generally done by using a mechanical testing machine and continuously measuring the force developed as the material is elongated at a constant rate of extension. Fig. 7.19 illustrates a typical stress–strain curve. Important mechanical properties of a material include the modulus (slope of the initial curve), which is a measure of the material stiffness; yield stress; strength; ultimate strength; elongation at break; and toughness (area under the curve).

For practical purposes, it is often useful to divide polymeric materials into five common classes depending on their stress–strain behavior. These common classes are illustrated in Table 7.1.

For polymer films, an increase in molecular weight tends to increase film tensile strength, elongation, and flexibility. This can be explained on the basis that longer polymer chains exhibit greater flexibility and elasticity. They can thus be extended further before rupture, as compared with short polymer chains.

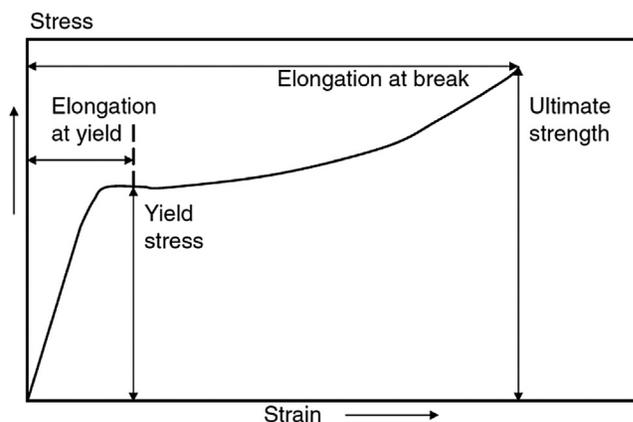


FIGURE 7.19 Typical tensile stress–strain curve for a polymer specimen tested in tension.

TABLE 7.1 Common Classes of Materials Based on Their Stress–Strain Curve Characteristics (Ref. 32)

Class	Modulus	Yield stress	Ultimate strength	Elongation at break
Soft and weak	Low	Low	Low	Moderate
Soft and tough	Low	Low	Moderate	High
Hard and brittle	High	None	Moderate	Low
Hard and strong	High	High	High	Moderate
Hard and tough	High	High	High	High

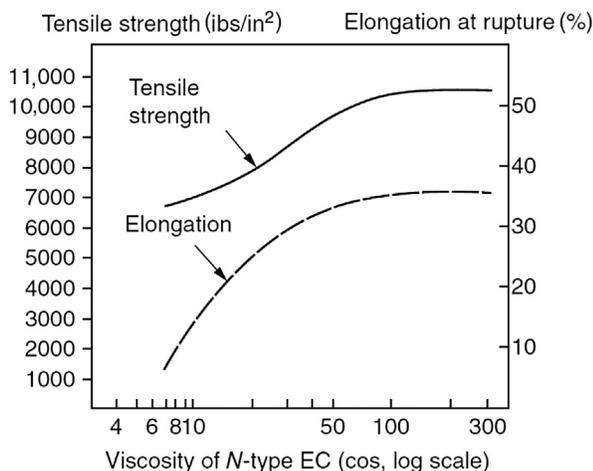


FIGURE 7.20 Ethyl cellulose film properties as a function of solution viscosity (molecular weight). All solutions viscosity values reflect 5 wt.% ethyl cellulose in an 80:20 blend of toluene:ethanol. Courtesy of Ashland Specialty Ingredients Wilmington, DE.

A general relationship describing this behavior is given by the following equation:

$$\text{Tensile strength} = a - \frac{b}{M_n}$$

where a is the tensile strength threshold, beyond which further molecular weight increases become ineffective; b is a material-dependent constant; and M_n is number average molecular weight.³² An example of this is given in Fig. 7.20, which shows the viscosity (MW) dependence of ethyl cellulose film properties.

Film strength is of significance in membrane reservoir controlled-release dosage forms such as multiparticulates or tablets coated with ethyl cellulose controlled-release films. It has been shown that the drug-release kinetics of such systems are directly proportional to the film strength and, by inference, polymer molecular weight (Fig. 7.21). This is due to the fact that the drug release from membrane-reservoir systems is osmotic pressure dependent. As the water enters the dosage forms via osmosis and builds up hydrostatic pressure in the core, it increasingly exerts a stress on the membrane until fissures and cracks open up, resulting in the release of the drug due to osmotic pumping.^{33–35}

Similar examples of increasing film strength with molecular weight are known for the majority of pharmaceutical polymers. A further example is the report by Prodduturi et al., describing the increased mechanical strength of drug-loaded buccal films with increasing molecular weight of HPC used.³⁶

7.2.6.1.4 Mechanical strength of tablets

As previously indicated, longer polymer chains impart greater elasticity, while the greater chain-end

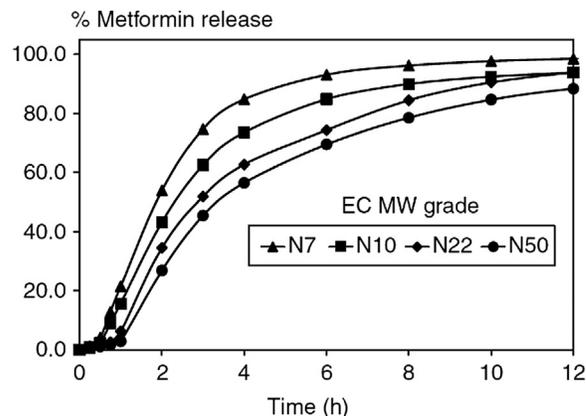


FIGURE 7.21 Drug release from metformin HCl pellets coated with various molecular weight grades of Ashland N Pharm ethyl cellulose (EC).³³ N7, N10, N22, and N50 refers to different molecular weight grades with 7, 10, 22, and 50 cps solution viscosity (5 wt.% solution in 80:20 toluene:ethanol), respectively.

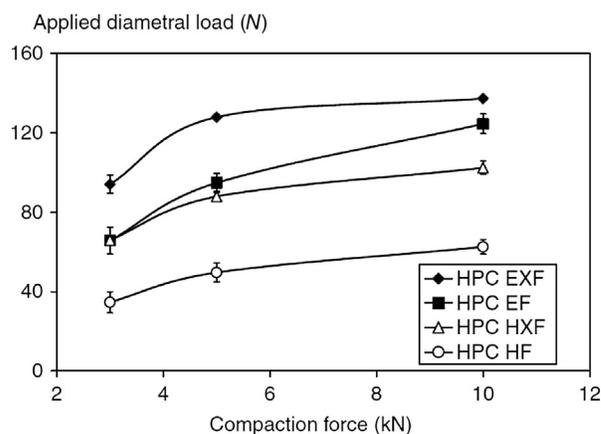


FIGURE 7.22 Compactability for various molecular weight and particle size types of hydroxypropyl cellulose. Klucel™ EXF Pharm HPC (80 kDA, 70 μm average particle size) Klucel™ EF Pharm HPC (80 kDA molecular weight, 200 μm average particle size), Klucel™ HXF Pharm HPC (1000 kDA molecular weight, 70 μm average particle size), Klucel™ HF Pharm HPC (80 kDA, 200 μm average particle size); 300 mg pure polymer tablets were compressed on a Manesty BetaPress using 7/16" round flat-faced tooling.

concentration found with decreasing molecular weight results in greater plasticity and molecular mobility. For directly compressed tablets, lower polymer molecular weight, therefore, results in less post-ejection elastic recovery and greater permanent deformation. For example, low-molecular-weight HPC grades have been reported to yield stronger tablets than high-molecular-weight HPC due to greater plasticity and lower postcompaction ejection.³⁷ However, this disadvantage of high-molecular-weight polymers can be partly neutralized by using fine-particle-size HPC (Fig. 7.22).³⁸ Similar observations have also been made for ethyl cellulose matrix tablets.³⁹

7.2.6.1.5 Glass transition temperature, melting point, and melt index

The glass transition temperature (T_g), melting point temperature, and melt index are fundamental characteristics related to thermoplastic behavior. Similar to mechanical properties, a negative inverse relationship has also been postulated for T_g and molecular weight⁴⁰:

$$T_g = T_g^\infty - \frac{k}{M_n}$$

where T_g^∞ is the glass transition at infinite molecular weight, and k is a constant. The greater flexibility and lower T_g of lower-molecular-weight polymers are attributed to the greater concentration and mobility of polymer chain ends versus the chain middle. Due to their greater mobility and the effective defect in material packing that they create, chain ends are associated with greater excess free volume. In a series of equally substituted polymers, lower-molecular-weight polymers will thus have a greater concentration of chain ends, resulting in greater excess free volume, greater molecular mobility, and a lower T_g . A good example of this is provided by poly(vinyl pyrrolidone) (PVP), a simple, linear, polymer molecule with additional side chains or cross-linking. Table 7.2 illustrates the inverse relationship between T_g and molecular weight. Additionally, Fig. 7.23 shows the change in T_g as a function of solution viscosity (as an indirect proxy for molecular weight) for a series of ethyl cellulose polymers.

T_g is an important fundamental property of amorphous and semicrystalline polymer systems, and it is frequently correlated with properties such as plasticity, ductility, film-forming ability, and stickiness. While polymer molecular weight is a major factor determining T_g values, numerous other structural factors will impact molecular rigidity and order, and, by implication, T_g . Some of these factors are summarized in Table 7.3.

Similarly to T_g , melting point temperatures and melt viscosity increase with increasing molecular

TABLE 7.2 Different Molecular Weights of PVP and Their Glass Transition Temperatures (T_g s)

Product	K value	M_w^a	T_g (°C)
Plasdone K12	10.2–13.8	4000	120
Plasdone K17	15.5–17.5	10,000	140
Plasdone K25	2.14–26	34,000	160
Plasdone K29/32	29–32	58,000	164
Plasdone K90	85–95	1,300,000	174

^aWeight average molecular weight.

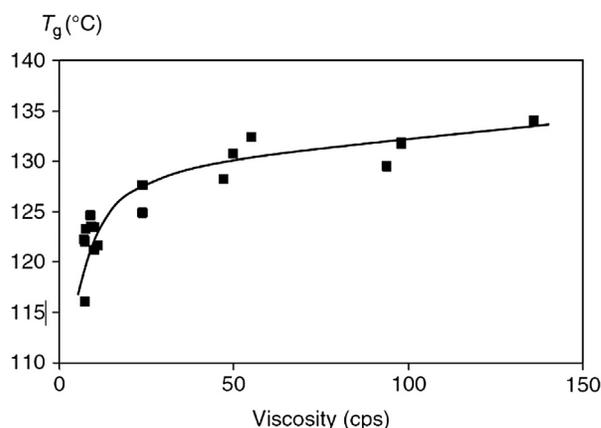


FIGURE 7.23 Glass transition temperature (T_g) as a function of solution viscosity (an indicator of molecular weight) for a series of Ashland ethyl cellulose polymers. In all cases, substitution was between 49.8 and 51 wt.% ethoxyl content.

TABLE 7.3 Factors Affecting Glass Transition Temperature (T_g) Values

Molecular structural feature	Impact on T_g
Increased molecular weight	Higher
Increased symmetry	Higher
Increased length of flexible side chain	Lower
Addition of chain-stiffening units	Higher
Addition of polar groups	Higher
Increased cross-link density	Higher

weight. Operationally, polymer flow is typically characterized using a melt flow index, which is an inverse measure of melt viscosity. These properties are especially critical in modified-release dosage form design in the context of thermal processing, such as melt extrusion and injection molding. Frequently, higher melt flow index polymers are required for thermal processing in the range at or below 100°C in order to avoid thermal degradation of drug and acceptable throughput rates. Fig. 7.24 shows the variation of melt flow indices for different molecular weight grades of HPC, a thermoplastic polymer that is commonly used in melt extrusion processes, such as the manufacture of oral film strips and other extruded drug delivery devices.

7.2.6.1.6 Effect of molecular weight on gel strength

The relationship between gel strength and polymer molecular weight is of particular importance in the field of modified-release dosage form design. For hydrophilic matrix tablets, the gel strength will determine the erodibility of the matrix system. Erosion can

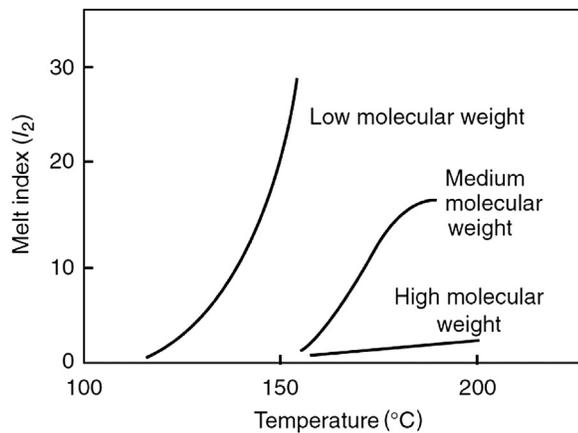


FIGURE 7.24 Melt index, I_2 , as a function of temperature and Klucel™ hydroxypropyl cellulose molecular weight. The melt index is defined as the grams of molten material that is extruded under standard American Society for Testing and Materials (ASTM)-defined conditions in 10 min at a given temperature and applied load.

be described as polymer dissolution or the disentanglement of polymer chains from the gel surface and transfer of the polymer to the bulk solution. Erosion can be used to the formulator's advantage when designing a delivery system for insoluble drugs. Here, erosion is the main mechanism facilitating transfer of the insoluble drug out of the tablet matrix and into the dissolution medium. However, poor release characteristics such as variable burst release and dose dumping may be expected for a highly soluble drug that is formulated in a highly erodible dosage form.

For hydrophilic polymers such as hypromellose and HPC compressed into matrix tablets, the disentanglement concentration of the polymer follows a nonlinear, inverse relationship with molecular weight.⁴¹ Furthermore, the polymer matrix erosion rate has also been shown to vary with the molecular weight in a nonlinear, inverse manner⁴²:

$$\text{Erosion rate} = kM_n^{-a}$$

It should be noted that the opposite relationship applies to matrix swelling, that is, swellability increases with molecular weight up to a limiting threshold level. The rate and extent of polymer matrix swelling and erosion and the drug solubility and concentration are the dominant compositional factors determining drug-release kinetics from matrix tablet systems. Figs. 7.25–7.27 show the impact of the polymer molecular weight on the matrix tablet erosion, swelling, and drug release for a typical sparingly soluble compound, nifedipine.

7.2.6.2 Side-chain substitution effects

The structure of the side-chain substituents on the polymer backbone is a major compositional factor

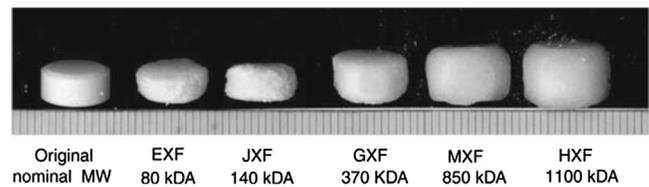


FIGURE 7.25 Effect of Klucel™ Pharm HPC molecular-weight grade on erosion and swelling behavior of nifedipine matrix tablets subjected to dissolution testing for 4 h. Formulation: 20% nifedipine, 30% HPC, 49.5% microcrystalline cellulose, and 0.5% magnesium stearate.

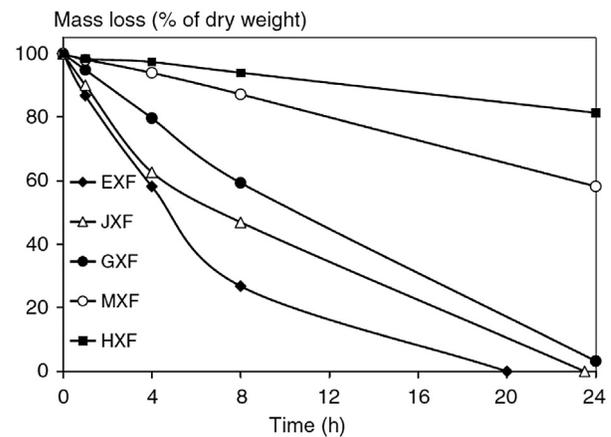


FIGURE 7.26 Effect of Klucel™ HPC molecular-weight grade on matrix erosion. Nominal molecular weights for Klucel™ EXF, JXF, GXF, MXF, and HXF Pharm HPC are 80, 140, 370, 850, and 1100 kDA, respectively. Formulation: 20% nifedipine, 30% HPC, 49.5% MCC, and 0.5% magnesium stearate.

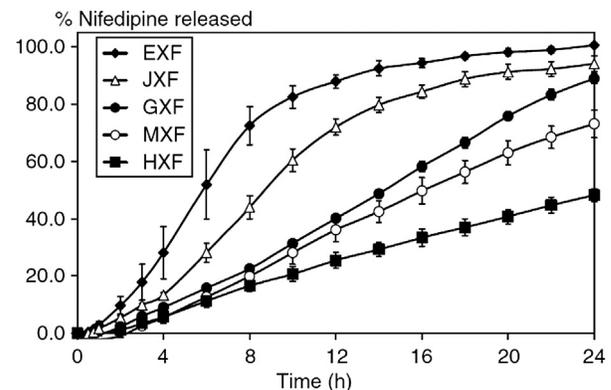


FIGURE 7.27 Effect of Klucel™ HPC molecular-weight grade on nifedipine dissolution. Nominal molecular weights for Klucel™ EXF, JXF, GXF, MXF, and HXF Pharm HPC are 80, 140, 370, 850, and 1100 kDA, respectively. Formulation: 20% nifedipine, 30% HPC, 49.5% MCC, and 0.5% magnesium stearate.

impacting polymer functionality. Important aspects of substitution are the chemical structure of the substituents, the extent of backbone substitution, and the uniformity of substitution. In this section, we will mainly focus on the impact of substituent type and the extent of substitution on the functionality in modified-release systems.

7.2.6.2.1 Side-chain structure (substituent type)

Effect of side-chain structure on polymer solubility. In most cases, substitution of less polar groups for hydrogens or hydroxyls on a polymer chain leads to a reduction in crystallinity and, usually, also a reduction in melting points. Such changes are thus generally expected to improve thermoplasticity and polymer solubility. A good example is presented by cellulose, a naturally occurring polymer comprised of anhydroglucose units. Native cellulose has considerable microcrystalline character. When the free hydroxyls on the anhydroglucose backbone are substituted with hydroxyalkyl side chains, for example, hydroxypropyl or hydroxyethyl groups, the crystallinity of the resultant hydroxypropyl or hydroxyethyl cellulose is below the limit of reliable quantification (<10%). Moreover, unlike microcrystalline cellulose, the derivatized cellulose ethers are freely gelling and soluble in water. Polymer water solubility can be further enhanced by deliberate inclusion of highly polar, ionizable substituents. Sodium carboxymethyl cellulose (NaCMC) is an example of this.

Unlike small drug molecules, it is not useful to describe the solubility of a polymer in a given solvent system in terms of saturation concentration values (eg, g/mL). Among the more useful methods, solubility parameters can be used to evaluate the solubility and compatibility between a polymer and solvent or other additives with solvent-like properties. Additionally, for water solubility, equilibrium moisture content (hygroscopicity) and cloud point are useful indirect measures of water solubility. The solubility parameters for a series of differently substituted cellulose ether molecules and other materials of interest to formulators are shown in Table 7.4.

For many polymers including cellulose, the relationship between water solubility and the nature of the side chain or substituent chemistry can be understood in terms of hydrogen bonding between the hydrogen atoms of water and the polar oxygen atoms present in the polymer backbone and on the side chains. Studying a series of alkali celluloses of similar molecular weight, Klug⁴³ showed that polymer hydrophilicity increases as the oxygen content of the derivatized cellulose increases due to either the type or the extent of substitution. Sodium carboxymethyl cellulose is an exception due to its ionic character. The increased

TABLE 7.4 Solubility Parameters for a Series of Cellulose Ethers and Other Materials of Interest

Polymer or drug molecule	Average solubility parameter, ^a δ (MPa ^{1/2})
EC (2.7 DS)	19.2
HPC (3.8 MS)	23.2
HPMC (1.9 MS)	23.6
HEC (2.5 MS)	25.0
NaCMC (0.7 DS)	28.9
Cellulose	31.1
PVA	30.2
PEO	19.3
Metformin HCl (highly water-soluble drug)	27.2
Itraconazole (low water-soluble drug)	19.5

^aCalculated as the Average of the Hildebrand, Hansen, Fedors, and van Krevelen Solubility Parameters.

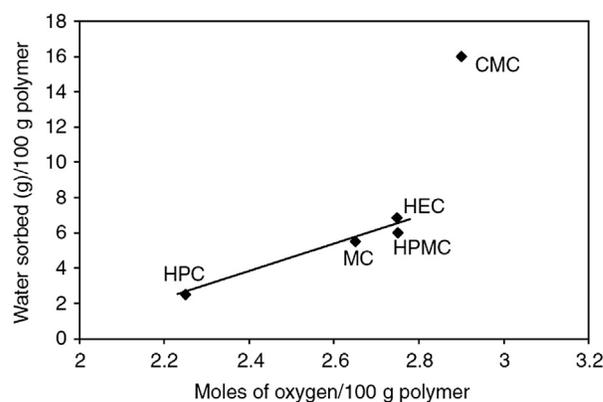


FIGURE 7.28 Effect of oxygen content on the equilibrium moisture content of a series of cellulose derivatives. HPC, hydroxypropyl cellulose; MC, methyl cellulose; HPMC, hydroxypropyl methylcellulose; HEC, hydroxyethyl cellulose; CMC, sodium carboxymethyl cellulose. Adapted from Klug, E.D. Some properties of water soluble hydroxyalkyl celluloses and their derivatives. *J Polym Sci Part C* 1971;36:491–508.

hydrophilicity impacts numerous important properties such as hygroscopicity, cloud point, matrix tablet swelling ability, and matrix gel strength. The general relationship is shown in Fig. 7.28.

Effect of side-chain structure on gel strength, swelling, and erosion in matrix systems. From Fig. 7.28, it can be seen that the differently substituted cellulose derivatives can be ranked in the following order of ascending hydrophilicity: HPC < MC < HPMC < HEC and CMC. The difference in hydrophilicity due to substitution on the polymer backbone is particularly important for the functionality of hydrophilic matrix systems. As shown in Fig. 7.29, polymer hydrophilicity, in combination

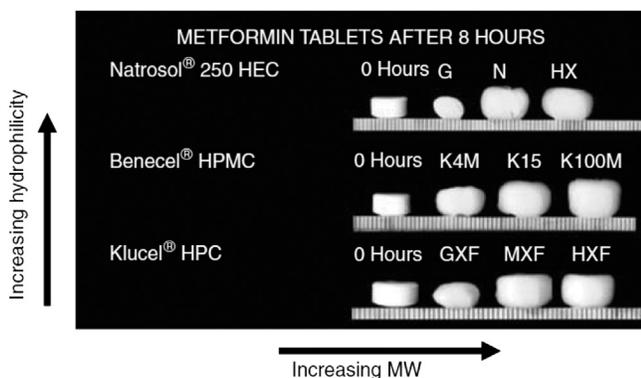


FIGURE 7.29 Matrix tablet swelling and erosion behavior as a function of hydrophilicity (cellulose ether substitution) and molecular weight.

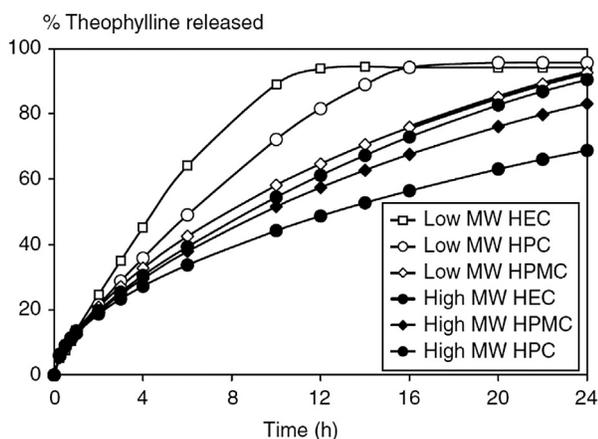


FIGURE 7.30 Drug release from matrix tablets as a function of cellulose ether chemistry and molecular weight.

with molecular weight, has a major impact on matrix swelling and erosion behavior. For medium and low-soluble drugs, these factors are the main determinants of release mechanism and release kinetics (Fig. 7.30).

Effect of side-chain structure on mechanical properties. The nature of the side-chain substituent type also significantly impacts mechanical and thermoplastic properties. HPC and ethyl cellulose (EC) are significantly more thermoplastic than HPMC and HEC. The compactibility of matrix-forming cellulose ethers has been reported to increase in the following rank order: HEC < HPMC < HPC.⁴⁴

7.2.6.2.2 Extent of side-chain substitution

In addition to the identity of the side-chain structure, the amount of side-chain substitution on the polymer backbone can also exert a significant effect on physical and chemical properties of the polymer.

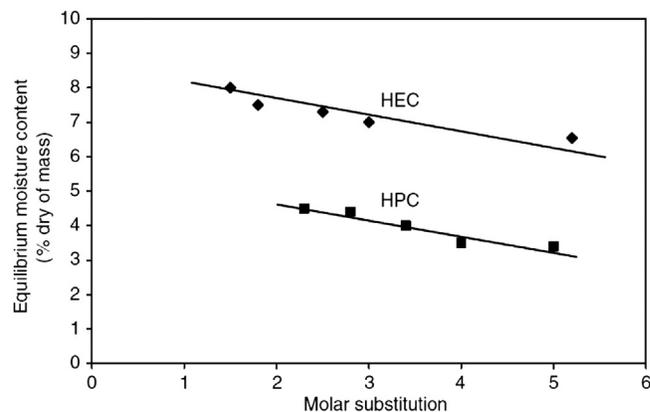


FIGURE 7.31 Effect of substitution level on the equilibrium moisture content of hydroxypropyl and hydroxyethyl cellulose at 50% relative humidity. Adapted from Klug, E.D. *Some properties of water soluble hydroxyalkyl celluloses and their derivatives*. *J Polym Sci Part C* 1971;36:491–508.

7.2.6.2.3 Effect of extent of substitution on solubility

When highly polar hydroxyl groups on crystalline cellulose are substituted with hydroxyalkyl groups to manufacture HPC or HEC, water solubility initially increases due to a reduction in crystallinity and hydrogen bonding between the cellulose backbone chains. However, as the amount of hydroxyalkyl substitution continues to increase, the polymer becomes increasingly hydrophobic. As shown in Fig. 7.31, the equilibrium moisture content steadily decreases as MS increases from 2.0 to 5.0 for both HEC and HPC. A similar relationship has also been demonstrated for the cloud point.⁴³ An exception to this behavior is polymers with ionic groups in their side chains. In this case, increasing the level of highly polar substituents will increase water solubility. For example, when the DS for sodium carboxymethyl cellulose is increased from 0.7 to 1.2, the equilibrium moisture content at 50% relative humidity increases from 13% to 18%.⁴³

7.2.6.2.4 Effect of extent of substitution on amorphous solid dispersion properties

As explained, the amount of side-chain substitution or the ratio of different substituents will affect the relative hydrophilic-hydrophobic balance of the polymer. When using polymers as carriers for amorphous solid dispersion of poorly soluble drugs, this has the potential to affect the polymers' ability to undergo hydrogen bonding with drug molecules in the solid state, as well as to undergo hydrophobic interaction with drug molecules in the saturated solution state. For example, as shown in Fig. 7.32, HPMCAS is available in three different acetyl/succinyl substitution ratios.

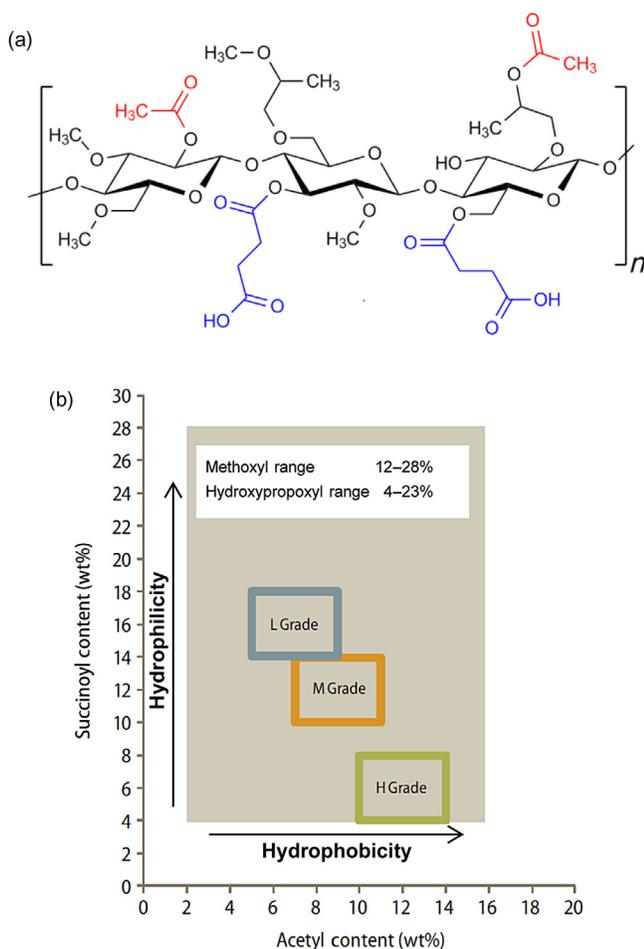


FIGURE 7.32 (a) Idealized chemical structure of HPMCAS. (b) Schematic showing acetyl and succinoyl substitution ranges and effect on hydrophilic/lipophilic balance for different commercial grades of Aquasolv™ HPMCAS.

These different substitution grades can stabilize amorphous solid dispersions to varying degrees, depending on drug properties. Fig. 7.33 shows that H grade is significantly better at preventing recrystallization of rapid recrystallizer ezetimibe in the solid amorphous state than M and L grade, both of which have higher succinoyl content. This can be related to the ability of HPMCAS H grade to undergo better hydrogen bonding.⁴⁵

In addition, the acetyl/succinoyl substitution level also affects precipitation inhibition in saturated drug solutions that occurs after the amorphous dispersion is dissolved. Fig. 7.34 shows that HPMCAS with high acetyl, that is, greater hydrophobicity, is more effective at preventing ezetimibe precipitation from saturated solutions. This can be related to an improved hydrophobic interaction and drug-polymer binding capability.⁴⁶

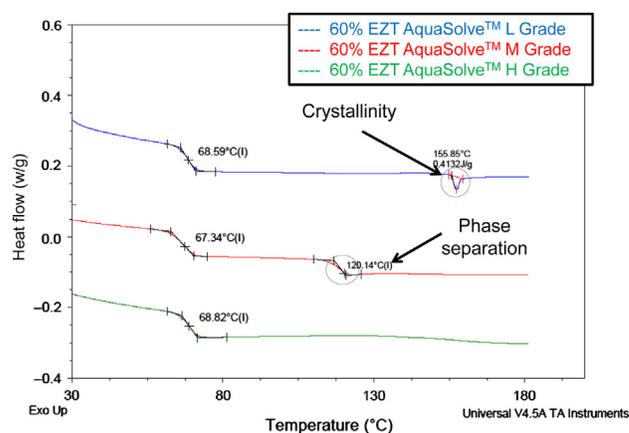


FIGURE 7.33 DSC thermograms for ezetimibe: Aquasolv™ HPMCAS solid dispersions aged for 65 h in open dish conditions at 40°C and 75% relative humidity.

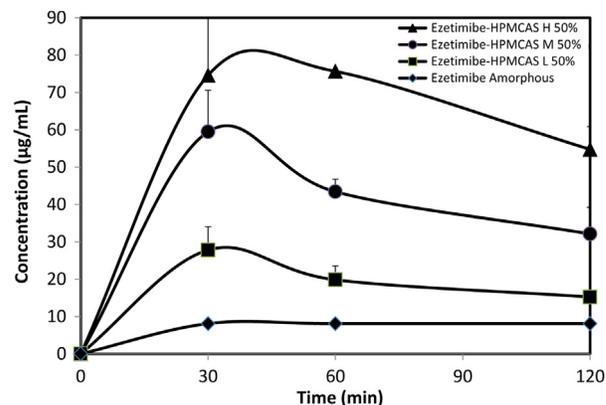


FIGURE 7.34 Nonsink condition dissolution profiles of amorphous ezetimibe and ezetimibe-Aquasolv™ HPMCAS solid dispersions equivalent to 500 µg/mL ezetimibe in 20 mL FaSSIF media at 37°C and 300 rpm using fiber-optic dissolution profiler, µDISS Profiler. At 30, 60 and 120 min, samples ($n = 4$) were centrifuged at 3700 rpm for 5 min, and the supernatant was analyzed for drug concentration.

7.2.6.2.5 Effect of extent of substitution on mechanical properties

In addition to increased hydrophobicity, an increase in the amount of less polar substituents generally also results in an increase in polymer plasticity. As shown in Fig. 7.35, in the case of tensile film strength, this manifests in lower ultimate tensile strength but greater elongation and film flexibility. In contrast, increasing the amount of highly polar, ionic side chains tends to result in an increased T_g , a markedly less thermoplastic material. As a result, films will tend to exhibit relatively high tensile strength but will be very brittle and inflexible, with minimal elongation at break. Sodium carboxymethyl cellulose shows this behavior and, as a result, requires high levels of added plasticizer if useful, defect-free films suitable for tablet or particle coating are to be achieved.

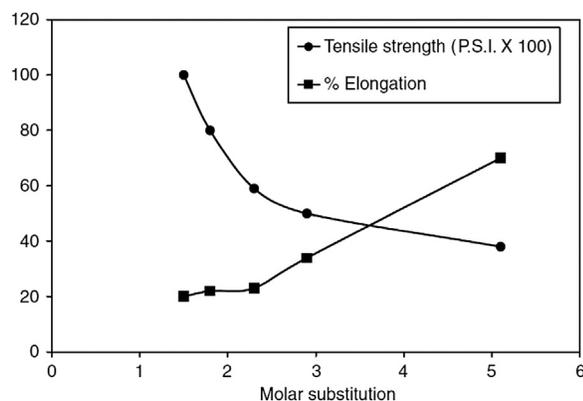


FIGURE 7.35 Effect of amount of substitution on the tensile strength and percentage elongation of a hydroxyethyl cellulose film at constant thickness, 50% relative humidity and 25°C. Adapted from Klug, E.D. *Some properties of water soluble hydroxyalkyl celluloses and their derivatives*. *J Polym Sci Part C* 1971;36:491–508.

TABLE 7.5 Tablet Tensile Strength for a Series of Hypromellose and Methyl Cellulose Samples of Similar Viscosity When Compressed at 15 kN⁴⁷

Polymer type	Methoxy (%)	Hydroxy propyl (%)	Tensile strength (MPa)
HPMC 2208	10–24	4–12	1.5
HPMC 2910	28–30	7–12	1.6
HPMC 2906	27–30	4–7.5	2.8
MC	27.5–31.5	0	3.5

For polymers compressed into tablets, increasing the number of nonpolar substituents generally results in increased plasticity, lower elastic recovery after compression and ejection, and consequently denser compacts with higher diametral crushing strength (tensile failure). Similarly, decreasing the number of more polar substituents will have the same effect. The compaction behavior of a series of hypromellose and methyl cellulose grades with varying levels of methoxyl (less polar, hydrophobic substituent) and hydroxypropyl (more polar, more hydrophilic substituent) groups illustrates this.⁴⁷ As can be seen in Table 7.5, as the percentage of methoxyl in the polymer increases and the percentage of hydroxypropyl decreases, for a series of similar viscosity polymers, the tablet strength significantly increases.

An additional example of the significant effect that an increase in the number of nonpolar substituents can have is provided by ethyl cellulose (EC). It has been reported that a higher compactability of EC was associated with high ethoxyl content and low molecular weight (low viscosity) (Fig. 7.36).⁹²

High substitution and low molecular weight were also correlated with significantly higher crystallinity

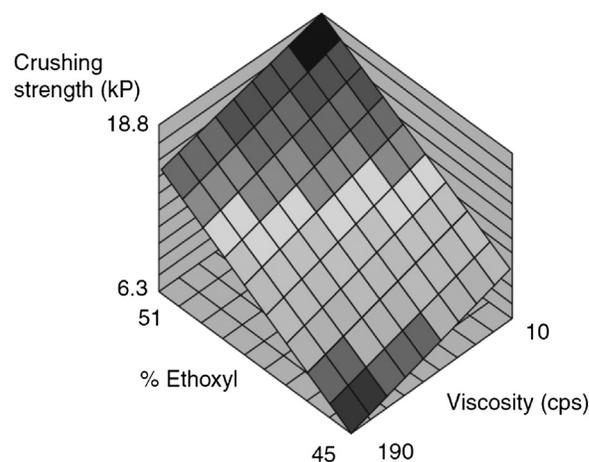


FIGURE 7.36 Effect of ethoxyl content and viscosity (molecular weight) on compactability of ethyl cellulose (EC). Maximum tablet strength is achieved for high ethoxyl, low viscosity EC.

TABLE 7.6 Effect of Ethoxyl Content and Viscosity on Selected Solid-State Properties of Ethyl Cellulose

Ethoxyl (wt.%)	Viscosity (cps)	Crystallinity (%)	Melting point (°C)	T _g (°C)	Crushing force (kP) ^a
50.4	9	24.6	257.0	122.1	20.9
50.8	9	28.5	261.1	124.6	18.8
50.0	50	15.3	246.6	130.7	14.6
49.6	94	17.8	261.0	129.5	16.1
48.0	10	9.1	210.0	131.0	14.7
48.5	94	7.9	224.3	133.5	11.5
47.5	10	8.2	178.6	135.1	12.3

^a275 mg pure ethyl cellulose tablets compressed on a Manesty BetaPress at 25 kN.

and higher melting points, while the amorphous regions had lower glass transition temperatures (Table 7.6). Compaction simulator studies showed that the net effect of this unique solid-state structure is a marked reduction in postcompaction elastic recovery of the polymer (Fig. 7.37). Less energy of compaction was therefore lost due to postcompaction axial expansion, resulting in denser compacts with lower porosity. This had a significant effect on drug diffusion from nonswelling, porosity-controlled matrix tablets. Additionally, the reduced viscoelasticity resulted in lower strain rate sensitivity (10% vs typically 20–25% for other EC types).

7.2.6.3 Copolymerization

7.2.6.3.1 Thermal properties of copolymers

When the monomers of two crystalline homopolymers are combined, the degree of crystallinity and the

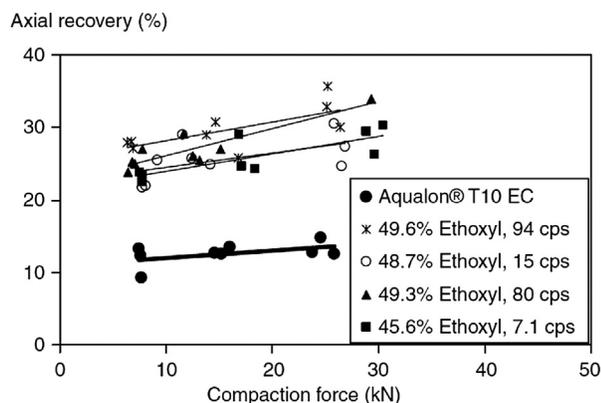


FIGURE 7.37 Effect of ethoxyl content and viscosity on postcompaction axial recovery. High ethoxyl, low-viscosity Ashland T10 EC has the lowest axial recovery.

melting point are usually depressed. The following relationship frequently applies:

$$\frac{1}{T_m} = \frac{1}{T_m^0} - \frac{R}{\Delta H_m} \ln(n)$$

where:

- n is the mole fraction of crystalline constituent;
- T_m is the melting point of the copolymer;
- T_m^0 is the melting point of the pure homopolymer;
- ΔH_m is the heat of fusion.²

In contrast, the glass transition temperature, T_g , of random copolymers usually falls into the range between that of the two corresponding homopolymers. This difference between how T_m and T_g of a copolymer are affected can be attributed to the fact that crystal structure disruption is not relevant to T_g of the amorphous polymer domains. Frequently, a simple weight-average mixing rule of the following type can be applied to get an approximate idea of the resultant T_g of the copolymer:

$$a_1 w_1 (T_g - T_{g1}) + a_2 w_2 (T_g - T_{g2}) = 0$$

where:

- T_{g1} and T_{g2} refers to the individual homopolymers;
- w_1 and w_2 are weight fractions of monomers 1 and 2;
- a_1 and a_2 depend on monomer type.⁴⁸

The 60:40 random copolymer of vinylpyrrolidone and vinyl acetate (copovidone) is a good example of this phenomenon. As shown in Fig. 7.38, the addition of vinyl acetate to vinylpyrrolidone results in a T_g of 105°C, which intermediate between polyvinylpyrrolidone (povidone) of similar molecular weight (165°C) and polyvinyl acetate (70°C) and a significant T_g reduction when compared to polyvinylpyrrolidone alone.

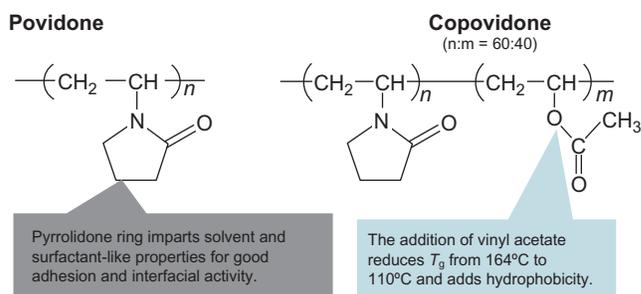


FIGURE 7.38 Schematic structures of povidone and copovidone.

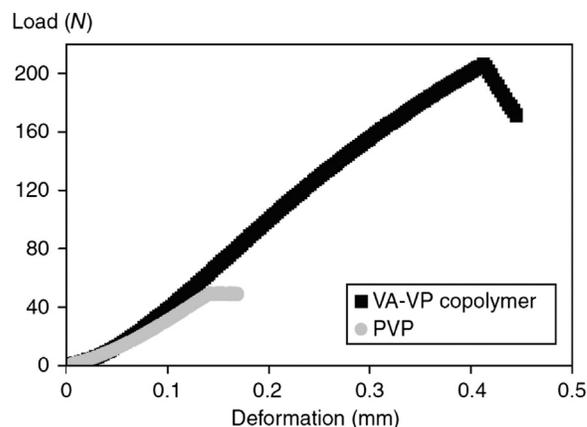


FIGURE 7.39 Load–deformation plots for the pure polymer tablets of povidone ($T_g \sim 161^\circ\text{C}$ and copovidone ($T_g \sim 101^\circ\text{C}$) subjected to diametral compression.

7.2.6.3.2 Mechanical properties of copolymers

The decrease in T_g and T_m as a result of adding a comonomer to an amorphous or crystalline generally results in an increase in copolymer plasticity and flexibility. Therefore, copolymers are frequently better film formers and tablet binders than the initial homopolymer. Povidone (PVP) and copovidone, the 6:4 random copolymer of vinylpyrrolidone and vinyl acetate (VP–VA copolymer) present a relevant pharmaceutical example. PVP, although frequently used as a tablet binder, is relatively stiff, brittle, and hygroscopic. The brittleness and stiffness are reflected in the relatively high T_g of approximately 164°C. In contrast, the VP–VA copolymer has a significantly lower T_g of approximately 110°C, is a lot more flexible and plastic, and has lower moisture uptake than PVP. This results in a significantly improved compactibility, as seen in Fig. 7.39.

7.3 COMMONLY USED POLYMER EXCIPIENTS IN SOLID ORAL PRODUCTS

Polymers are widely used as excipients or sometimes even active ingredients in pharmaceutical applications. The selection of excipients for a particular

application will depend on the therapeutic target, route of administration, dosage forms, and drug-release profile, in addition to the cost, availability, and complexity of related pharmaceutical unit operations.

The basic architecture of polymeric excipient materials to be considered consists of a relatively simple linear polymer structure. This includes cellulosic derivatives and most major synthetic polymers used as formulation components. Aside from a limited number of cross-linked polymers such as croscarmellose, lightly cross-linked poly (acrylic acid) (Carbopol), and crospovidone, most polymeric materials used as excipients are not branched or cross-linked. However, a number of materials do participate in reversible self-association that can result in the formation of dynamically branched or physically cross-linked system, and this secondary association equilibrium can exert an influence on the usage properties of the material.

Polymeric excipients are numerous and very diverse of natural, semisynthetic, or synthetic origin, depending on the source and method of preparation. They can be classified according to their source of origins: natural polymers and synthetic polymers. They can also be classified alternatively according to their chemical composition, chain shape, comonomer sequence, and their performance.

Biopolymers or natural polymers refer to polymers of natural origin, such as polysaccharides. They are produced by living organisms or from biomass derived from monomers such as sugars for polysaccharides. Natural polymeric materials such as shellac, amber, and natural rubber have been in use for centuries. A variety of other natural polymers exist, such as cellulose and hydrocolloids. Natural polymers can also be chemically modified to produce semisynthetic polymers. Commercially important semisynthetic polymers include ethyl cellulose (EC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and methyl cellulose (MC) for pharmaceutical applications.

Synthetic polymers are man-made by chemical synthesis from monomers. Polyacrylates, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), poly(lactico-glycolic acid) (PLGA), poly(ethylene glycol) (PEG), and polyethylene (PE) are typical examples of synthetic pharmaceutical polymers. Synthetic and semisynthetic polymers have a potential advantage over natural polymers due to their consistency and reproducibility in quality and functional properties.

Rather than presenting a comprehensive coverage of the molecular properties of all classes of polymeric excipients used in pharmaceutical formulations, we will focus our attention primarily on an overview of

those typically used in solid oral drug products. These polymeric excipients are used to fulfill a variety of functions in solid oral dosage forms such as binders, disintegrants, coatings, and drug-release, rate-controlling polymers.

The chemical structure and applications of a number of important pharmaceutical polymer excipients for oral dosage forms are shown in [Table 7.7](#).

7.3.1 Cellulose and cellulose derivatives

Cellulose is abundant in nature and exists in plant-based foods. It is a safe material for oral drug formulations based on a long history of human consumption. Cellulose and its derivatives (ether and ester) ([Fig. 7.40](#)) are among the excipients most frequently used in solid oral dosage forms. A number of overviews of polysaccharide chemistry in general,⁴⁹ and cellulose derivatives in particular,⁵⁰ are readily available, and these classic references remain worthwhile resources towards understanding key aspects of the chemistry.

The simplest modification of cellulose is size reduction. Powdered cellulose is produced by the purification and mechanical size reduction of α -cellulose obtained as a pulp from fibrous plant materials. It occurs as a white or almost white, odorless, and tasteless powder of various particle sizes, ranging from a free-flowing fine powder or granular dense powder to a coarse, fluffy, nonflowing powder. Powdered cellulose is used as a tablet diluent and filler in two-piece hard capsules.^{51,52} Powdered cellulose has acceptable compression properties. Low-crystallinity powdered cellulose has exhibited properties that are different from standard powdered cellulose materials, and it has shown potential as a direct-compression excipient. In soft gelatin capsules, powdered cellulose may be used to reduce the sedimentation rate of oily suspension fills. It is also used as the powder base material of powder dosage forms and as a suspending agent in aqueous suspensions for peroral delivery. It may also be used to reduce sedimentation during the manufacture of suppositories.

In order to improve the compactability of cellulose and make it useful as dry binder for roller compaction and tableting by direct compression, cellulose is modified by controlled hydrolysis with dilute mineral acid solutions of α -cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration, and the aqueous slurry is spray dried to form dry, porous particles of a controlled size distribution and moisture content for different applications. This process converts cellulose to microcrystalline cellulose (MCC). MCC is purified, partially depolymerized cellulose that occurs

TABLE 7.7 List of Polymeric Excipients for Oral Dosage Forms

Polymers	Major functionality	Applications	Typical use levels (%)	IID or IIG limit ^a
WATER-INSOLUBLE NATURAL/MODIFIED POLYMERS				
Cellulose, microcrystalline (MCC) (C ₆ H ₁₀ O ₅) _n , <i>n</i> ~ 220	Binder/filler	Tablet and capsules	10–90	789.6 mg
Cellulose, powdered (C ₆ H ₁₀ O ₅) _n	Filler	Tablet and capsules	5–40	391.7 mg
Cellulose, silicified, microcrystalline (SMCC), (C ₆ H ₁₀ O ₅) _n , SiO ₂	Binder/filler	Tablet and capsules	10–90	N/A
Cellulose acetate (CA) (C ₆ H ₇ O ₂ (OH) ₃) _n	Coating for osmotic pump	Osmotic pump	1–20	47.49 mg
Ethyl cellulose (EC) C ₁₂ H ₂₂ O ₆ (C ₁₂ H ₂₂ O ₅) _n C ₁₂ H ₂₃ O ₅	Coating/binder	Extended-release coating/matrix former	1–30	308.8 mg
Croscarmellose sodium (NaCMC) (C ₈ H ₁₆ O ₈) _n	Disintegrant	Tablet and capsules	0.5–25	180 mg
Sodium starch glycolate (SGS) (C ₂₄ H ₄₄ O ₆ Na) _n	Disintegrant	Tablet and capsules	2–8	876 mg
WATER-INSOLUBLE SYNTHETIC POLYMERS				
Crospovidone (C ₆ H ₉ NO) _n	Disintegrant	Tablet and capsules	2–30	340 mg
Polyacrylic acid (carbomer; Carbopol), (C ₃ H ₄ O ₂) _n	Rheology modifier/controlled release	Tablets, suspension	0.1–30	90 mg
Polymethacrylate, cationic	Coating/binder	Extended-release coating/matrix former	5–50	161 mg
Polymethacrylate, neutral	Coating/wet binder	Extended-release coating/matrix former	5–50	187.3 mg
WATER-SOLUBLE NATURAL/MODIFIED NATURAL POLYMERS				
Hydroxyethyl cellulose (HEC) [C ₆ H ₇ O ₂ (OH) _x (OC ₂ H ₅) _y [O(CH ₂ CH ₂ O) _m H] _z] _n	Coating/rheology modifier	Tablet, suspension, pellets	2–50	400 mg
Hydroxypropyl cellulose (HPC) (C ₃₆ H ₇₀ O ₁₉) _n	Binder/coating/controlled-release matrix, extrusion aid	Tablet, capsules, pellets	1–50	240 mg
Hydroxypropyl methylcellulose (HPMC or hypromellose) (C ₅₆ H ₁₀₈ O ₃₀) _n	Binder/coating/controlled-release matrix	Tablet, capsules, pellets	1–75	480 mg
Methyl cellulose (MC) C ₆ H ₇ O ₂ (OH) _x (OCH ₃) _y	Coating/binder/rheology modifier	Tablet, suspension, capsules	0.5–20	30 mg
Sodium alginate (C ₆ H ₇ O ₆ Na) _n	Coating/controlled-release matrix/rheology modifier	Tablet, capsules, pellets	1–40	350 mg
Sodium carboxymethyl cellulose (NaCMC) (C ₈ H ₁₅ NaO ₈) _n	Binder/coating/controlled-release matrix/rheology modifier	Tablet, capsules, pellets	0.1–90	2000 mg
WATER-SOLUBLE SYNTHETIC POLYMERS				
Polyethylene glycol (PEG), C _{2n} H _{4n+2} O _{n+1}	Plasticizer, solubility enhancer	Coating, tablet, softgel, capsules	1–40	960 mg
Polyethylene oxide (PEO), C _{2n} H _{4n+2} O _{n+1}	Mucoadhesion, tablet binder, matrix former, thickener	Tablets, coating	5–50	393.46 mg
Polyvinyl alcohol (PVA), (C ₂ H ₄ O) _n	Film former, thickener	Tablets, coating, microspheres	0.5–20	79.4 mg
Polyvinylpyrrolidone (PVP), (C ₆ H ₉ NO) _n	Coating, binder, solubility enhancement	Tablet, capsules, pellets	0.5–90	853.8 mg
POLYMERS WITH pH-DEPENDENT WATER SOLUBILITY				
Cellulose acetate phthalate (CAP)	Enteric coating	Tablet and capsules	0.5–9	75.6 mg
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	Enteric coating, solubility enhancement	Tablet and capsules	0.5–90	560 mg
Polymethacrylate, anionic	Enteric coating, solubility	Enteric coating, solubility	0.5–30	430.8 mg

^aFor the latest IID or IIG Limit: <http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>.

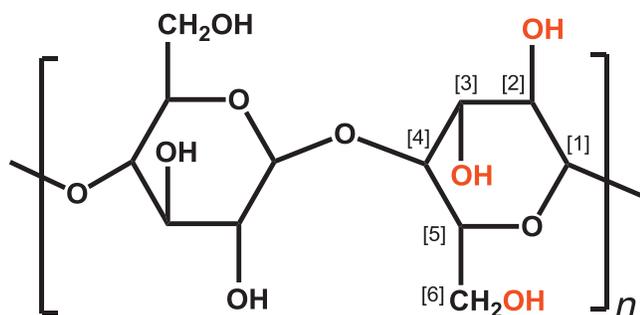


FIGURE 7.40 Basic structure of cellulose, which is used as the starting material for any cellulosic derivative. Each anhydroglucose residue possesses three potentially reactive hydroxyl groups. These are indicated and numbered in the second residue according to the associated carbon on which they reside. For most reaction schemes, the 2 and 6 positions are more reactive than the 3 position.

as a white, odorless, tasteless, crystalline powder composed of porous particles. The properties and applications of MCC depend on the particle sizes and moisture grades of MCC.^{53–55} MCC is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, MCC also has some lubricant and disintegrant properties that make it useful in tableting. A comparison of tensile strength of tablets made from different materials at various solid fractions is shown in Fig. 7.41 where it can be seen that microcrystalline cellulose is the most compactable filler. Therefore, it is not surprising that MCC has been a widely used excipient for tablets.^{56–60}

Cellulose can also be mixed with other ingredients to form coprocessed excipients. One of the most widely used coprocessed cellulose is silicified microcrystalline cellulose (SMCC).^{62–64} Silicified microcrystalline cellulose is a synergistic, intimate physical mixture of two components: microcrystalline cellulose and colloidal silicon dioxide. It is manufactured by cospray drying a suspension of microcrystalline cellulose particles and colloidal silicon dioxide such that the dried finished product contains 2%w/w colloidal silicon dioxide. The colloidal silicon dioxide appears physically bound onto the surface and inside the silicified microcrystalline cellulose particles. Extensive studies using different spectroscopic methods have not detected any form of chemical interaction.

Cellulose has also been coprocessed with lactose, mannitol, and sodium carboxymethyl cellulose for applications in direct compression for tablets as binder/filler and in oral suspensions as a suspension vehicle.

In order to improve the chemical and physical properties of cellulose for food and pharmaceutical applications, chemical modifications have been applied

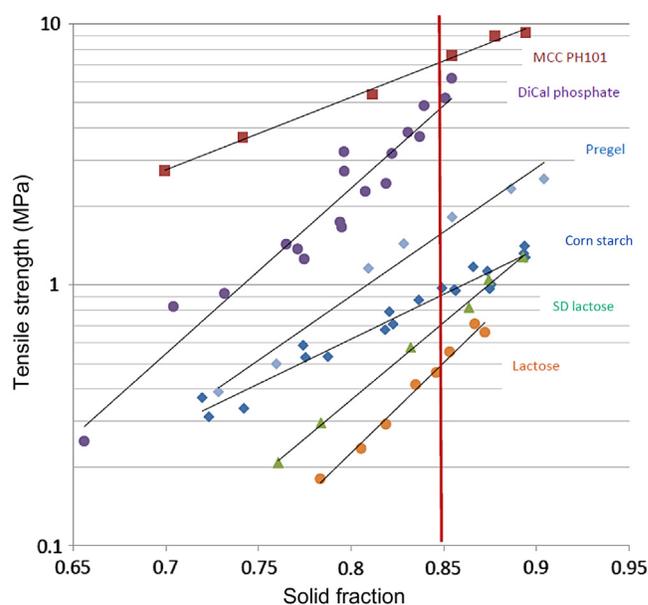


FIGURE 7.41 Comparison of tensile strength of tablets made from different materials at a solid fraction of 0.85, an average value for commercial tablets. Adapted from Amidon, G.E. *Compaction and the properties of mixtures*, presented at *Compaction Simulation Forum*, Cambridge, MA, November 13–14, 2012, <http://people.clarkson.edu/~cetinika/CompactionPresentation/1%20Amidon%20UMichigan.pdf>.⁶¹

to cellulose to produce a diverse range of cellulose derivatives for pharmaceutical applications.

As the name implies, cellulose derivatives are all based on cellulose provided by a variety of starting furnishes (wood pulp, chemical cotton). The starting biopolymer, cellulose, is a β -1–4 linked linear polymer of anhydroglucose (Fig. 7.40). Due to the relatively stiff main chain backbone, the array of available hydrogen bonding sites per monomer residue, and structural order inherent in the natural system, cellulose molecules form crystalline microfibrils that are mechanically strong and highly resistant to enzymatic attack. Cellulose is, therefore, insoluble in water and indigestible in the human body. Dissolution of cellulose normally requires exotic solvent systems or in situ derivatization to cap self-associating hydroxyl groups.

The reaction chemistry used in the production of cellulosic derivatives⁵⁰ is based on removing that hydrogen bond-mediated order from the system via activation of purified cellulose with a strong caustic, followed by reaction with appropriate alkylating agents (typically alkyl halides) and/or etherifying agents (eg, propylene oxide or ethylene oxide) to introduce various hydrophilic and/or hydrophobic substituents. This derivatization reaction introduces point-packing defects along the main backbone and prevents the reestablishment of the higher level of order that was present in the native cellulose. The overall result is that the material is rendered soluble in a

TABLE 7.8 Structure of Cellulose and Its Derivatives Based on Fig. 7.40

Cellulose derivatives	R groups
Cellulose	–H
Methyl cellulose (MC)	–H and –CH ₃
Ethyl cellulose (EC)	–H and –CH ₂ CH ₃
Hydroxyethyl cellulose (HEC)	–H and –CH ₂ CH ₂ OH
Hydroxypropyl cellulose (HPC)	–H and –CH ₂ CHOHCH ₃
Hydroxypropyl methylcellulose (HPMC)	–H and –CH ₃ and CH ₂ CHOHCH ₃
Hydroxypropyl methylcellulose acetate succinate (HPMC AS)	–H and –CH ₃ and CH ₂ CHOHCH ₃ , –C(O)CH ₃ , –C(O)CH ₂ CH ₂ COOH
Cellulose acetate	–H, –C(O)CH ₃
Cellulose acetate phthalate	–H, –C(O)CH ₃ , –C(O)C ₆ H ₄ COOH
Sodium carboxymethyl cellulose (Na CMC)	–H and –CH ₂ COONa

variety of solvents, with the preferred solvents being dependent on the substituents bound to the backbone. The overall molecular weight of the cellulose derivative is largely controlled by the specific selection of starting cellulose furnish for the higher-molecular-weight grades, with either in situ or post-derivatization oxidative or hydrolytic glycosidic chain scission being used to prepare the lower-molecular-weight members of a given chemical class (Table 7.8).

Much of the solution chemistry of cellulose derivatives can be organized by understanding the interplay of the substituent as a defect in the native cellulose packing structure to increase solubility with the use of substituent hydrophobicity and/or charge to tailor compatibility with nonaqueous or binary water/nonaqueous solvents.

Cellulose derivatives can be further classed according to whether or not the substituents can undergo a chain extension oligomerization (either in free solution or once grafted onto the cellulose backbone). Hydroxypropyl and hydroxyethyl substituents are able to undergo chain extension through the inherent hydroxyl group, whereas carboxymethyl, methyl, and ethyl substituents effectively cap the reactive hydroxyl site when they are grafted onto the chain. In cases where the substituent is able to undergo chain extension, the degree of substitution (DS = number of substituent capped hydroxyls per anhydroglucose) and total molar substitution (MS = number of substituent moles per mole of anhydroglucose) will differ with MS > DS. Note, for any cellulose derivative, the maximum value for DS cannot exceed three, as each

anhydroglucose unit only has three hydroxyl groups available for reaction (ie, DS < 3), whereas the MS can be greater than 3. For example, for most water-soluble cellulose ethers, the DS values are in the range of 0.4–2, whereas for water-insoluble polyether such as ethyl cellulose, the DS values are between 2.3 and 2.8. On the other hand, typical MS values for hydroxyalkyl ethers of cellulose are between 1.5 and 4.0.

Cellulose derivatives are generally graded according to their viscosity under defined concentration conditions, which is ultimately tied to their molecular weight and substitution levels as expressed by the DS, MS, or percent mass of grafted substituent. Note that in some cases (ethyl cellulose would be a specific example), the substituent used to quantify the mass loading of derivatizing reagent on the polymer, –OCH₂CH₃, reflects the combination of the oxygen atom from anhydroglucose with the ethyl group from the ethyl chloride used in the derivatization reaction. Typical data of the various grades of cellulose ethers shown in Table 7.9 indicate that the range in average molecular weight represented in these polymers is extremely large—ranging from 50,000 Da on the low side to 1,200,000 Da for the highest molecular weight materials available. This is a factor of 24 in net molecular weight. Owing to the variable content in residue formula weight provided by the pendant groups, a direct comparison of the differences in the DP will differ slightly. In this case, net degrees of polymerization, basically the number of discrete monomer residues on average per chain, range from a low of roughly 215 for low-molecular-weight sodium carboxymethyl cellulose to a high of about 4700 for the highest molecular weight grade of hydroxyethyl cellulose. Again, the total dynamic range that chain length varies is by about a factor of 20.

The broad range in the average molecular weight, or equivalently, the DP, tells only part of the story. These ranges reflect the wide variability in the population average values. Within a given population, in other words, for a given molecular weight, there is also a very disparate population of overall chain lengths present. For example, in a size exclusion chromatographic characterization of any of the high-molecular-weight celluloses, the net range of molecular weights encompassed by the population of a given moderate- to high-molecular-weight sample will typically span a range from a few hundreds to thousands up to a few million. In other words, the net diversity in chain lengths is extremely broad and easily spans a net range of two to three orders of magnitudes as the high- and low-molecular-weight portions of the distribution are accounted. A typical example is shown in Fig. 7.42. More typically, the polydispersity of a polymeric material is quantified by the ratio M_w/M_n . In cellulose

TABLE 7.9 Viscosity Grade Molecular Weights for Various Cellulose Derivatives

Viscosity grade (cP, at listed concentration)	Concentration (wt.%)	Viscosity measurement conditions	Approximate molecular weight (M_w , Daltons)
HYDROXYPROPYL CELLULOSE (HYDROXYPROPYL MS ~3.4–4.1)			
1500–3000	1	Brookfield (30 rpm/spindle 3)	1,150,000
4000–6500	2	Brookfield (60 rpm/spindle 4)	850,000
150–400	2	Brookfield (60 rpm/spindle 2)	370,000
150–400	5	Brookfield (60 rpm/spindle 2)	140,000
75–150	5	Brookfield (30 rpm/spindle 1)	95,000
300–600	10	Brookfield (30 rpm/spindle 2)	80,000
HYDROXYETHYL CELLULOSE (HYDROXYETHYL MS ~2.5)			
3500–5500	1	Brookfield (30 rpm/spindle 4)	1,300,000
1000–2500	1	Brookfield (30 rpm/spindle 3)	1,000,000
4500–6500	2	Brookfield (60 rpm/spindle 4)	720,000
250–400	2	Brookfield (60 rpm/spindle 2)	300,000
75–150	5	Brookfield (30 rpm/spindle 1)	90,000
HYDROXYPROPYL METHYLCELLULOSE (K TYPE (19–24 WT.% METHOXYL), E TYPE (28–30 WT.% METHOXYL), 7–12 WT.% HYDROXYPROPYL)			
160,000–240,000	2	Ubbelohde, too high for reliable measurement	1,200,000
80,000–120,000	2	Ubbelohde	1,000,000
19,200–36,000	2	Ubbelohde	675,000
11,250–21,000	2	Ubbelohde	575,000
3000–5600	2	Ubbelohde	400,000
SODIUM CARBOXYMETHYL CELLULOSE (NOMINAL CARBOXYMETHYL DS LEVELS OF 0.7, 0.9, 1.2)			
1500–3000	1	Brookfield (30 rpm/spindle 3)	725,000
1500–3100	2	Brookfield (30 rpm/spindle 3)	395,000
400–800	2	Brookfield (30 rpm/spindle 2)	250,000
25–50	2	Brookfield (60 rpm/spindle 1)	90,500
50–200	4	Brookfield (60 rpm/spindle 2)	49,000
ETHYL CELLULOSE (STANDARD OR N TYPE (48.0–49.5 WT.% ETHOXYL), T TYPE (49.6–51.0 WT.% ETHOXYL))^A			
80–105	5	Ubbelohde 2C	215,000
40–52	5	Ubbelohde 2	160,000
18–24	5	Ubbelohde 2	140,000
12–16	5	Ubbelohde 1B	120,000
8–11	5	Ubbelohde 1B	75,000
6–8	5	Ubbelohde 1C	65,000

^AEstimated, based on viscosity data.

derivatives, depending on type and viscosity grade, this ratio can range from 3 to values of 20 or so.

Typical examples of commonly used cellulose ethers and esters include the following⁶⁵:

7.3.1.1 Hydroxypropyl cellulose

HPC is an ether of cellulose where some of the hydroxyl groups on the cellulose backbone have been hydroxypropylated (Fig. 7.43).

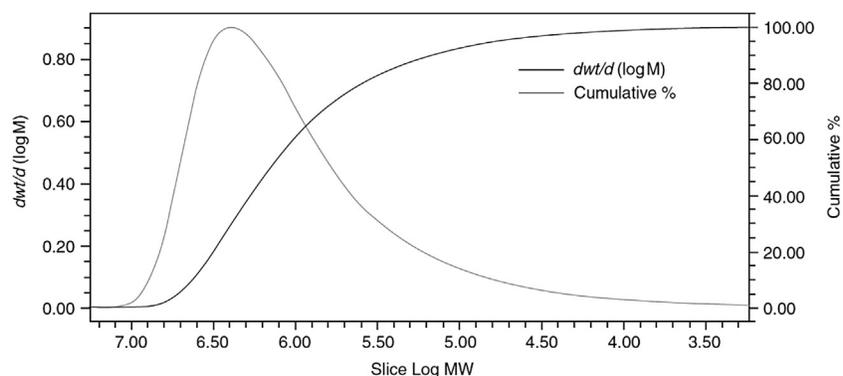


FIGURE 7.42 Representative molecular weight distribution profile of a high-viscosity grade (1500–3000 cP, 1% solution in water) sample of HPC. The molecular weight scale calibration in this example refers to narrow distribution polyethylene oxide/polyethylene glycol. Note that in this example, the net range of material spans roughly 2000–10,000,000 Da from the start to the end of the complete molecular weight distribution. This is a fairly typical situation for high-molecular-weight polymers.

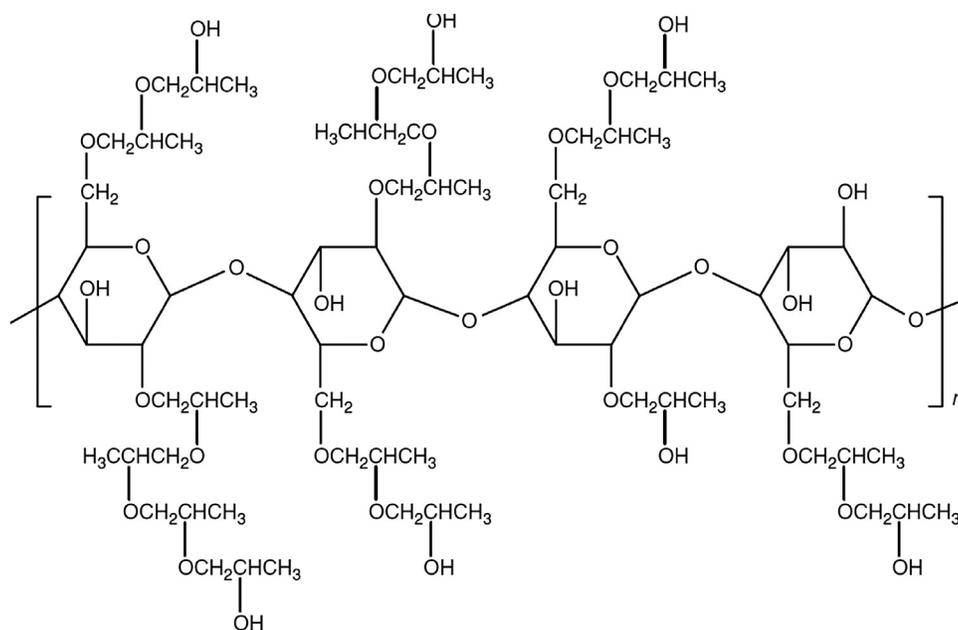


FIGURE 7.43 Typical structure for hydroxypropyl cellulose. The net molar substitution in this example is 4.0. Note that there is a distribution in the hydroxypropyl chain length for the pendant groups added to the base cellulose polymer. The relatively high hydroxypropyl content yields a somewhat hydrophobic thermoplastic polymer, which is sparingly soluble in hot water.

As mentioned earlier, because each of the added hydroxypropyl group introduces a secondary hydroxyl group, this can also be etherified during the preparation of HPC, giving rise to additional chain extension. When this occurs, the number of moles of hydroxypropyl groups per anhydroglucose ring, the molar substitution MS, will be higher than the degree of substitution DS (Fig. 7.43). To overcome the crystallinity of cellulose, HPC usually needs to have a MS about 4 in order to produce good solubility in water. Due to the high level of hydroxypropylation (around 70%), HPC is relatively hydrophobic, so it exhibits a LCST at 45°C. At temperatures below the LCST, HPC is readily

soluble in water; however, above the LCST, HPC is not soluble. HPC is widely used in solid oral dosage forms as a binder, a film coating, controlled-release matrix former, and as extrusion aid. HPC is commercially available in six different viscosity grades corresponding to average molecular weights from 80,000 to 1,150,000 Da (Table 7.9).

7.3.1.2 Hydroxypropyl methylcellulose

Hydroxypropyl methylcellulose (HPMC or hypromellose) is a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose ether derivative (Fig. 7.44).

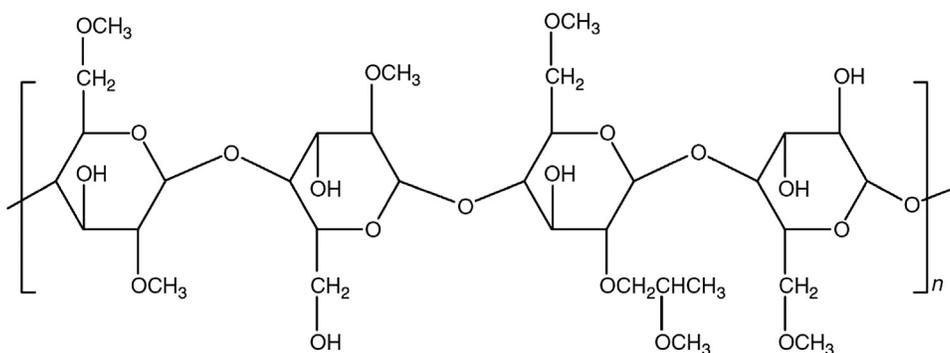


FIGURE 7.44 Typical structure for hydroxypropyl methylcellulose. This is an example of a mixed derivatized cellulose containing both hydroxypropyl and methoxyl functionality. The specific system shown has a hydroxypropyl DS of 0.25 (~9.6 wt.%) and methoxyl DS of 1.5 (~23 wt.%). Due to the lower content of bound hydrophobic functionality relative to HPC shown in Fig. 7.38, this material will generally display better water solubility at higher temperatures.

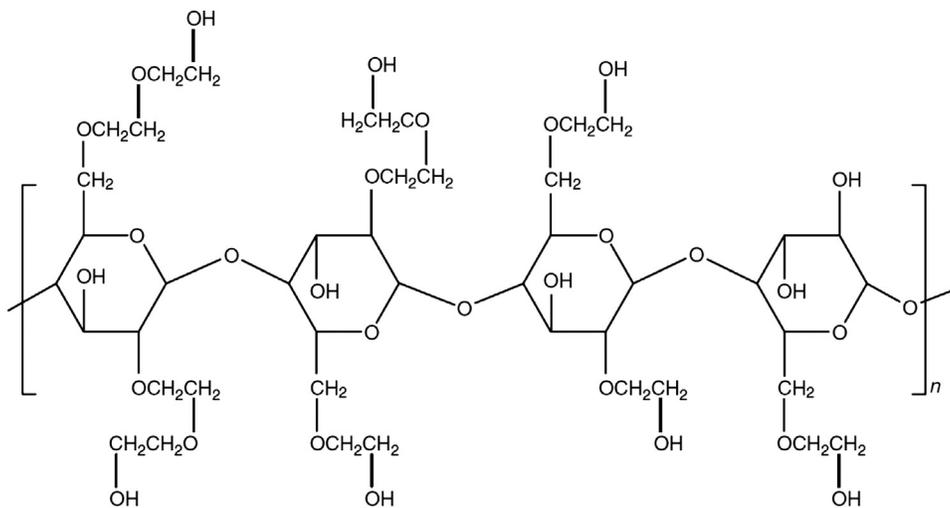


FIGURE 7.45 Typical structure for hydroxyethyl cellulose. As with hydroxypropyl cellulose, a distribution in hydroxyethyl oligomer chain lengths exists. In this example, the hydroxyethyl cellulose segment shown has a net molar substitution (MS) of 2.5, while the degree of substitution (DS) is 1.75 (=7/4).

HPMC is also widely used in solid oral dosage forms as a binder, a film coating, and a controlled-release matrix.^{66,67} It is often the polymer of choice in the preparation of hydrophilic matrix tablets because of its rapid formation of a uniform, strong, and viscous gel layer, which protects the matrix from disintegration and controls the rate of drug release. It is commercially available in several types with different DS and MS; here the added hydroxypropyl group introduces a secondary hydroxyl group that can also be etherified during the preparation of HPMC, giving rise to additional chain extension. Currently, the USP/NF and other compendia provide definitions for different substitution types of HPMC using a four-digit number: for example, hypromellose 2208, hypromellose 2906, and hypromellose 2910, respectively, where the first two digits refer to the approximate percentage content of the more methoxy group (OCH₃), and the second two digits refer to the approximate percentage content of the more hydroxypropoxy group

(OCH₂CH(OH)CH₃). Such variations in the ratios of methoxy and hydroxypropoxy substitutions and molecular weight affect their properties such as organic solubility, thermal gelation temperature in aqueous solution, swelling, diffusion, and drug-release rate. In practice, hypromellose 2208 (also known as K chemistry or grade) and hypromellose 2910 (also known as E chemistry or grade) are the most widely used types of HPMC in modified-release formulations. These two types of HPMC are commercially available in many different viscosity grades corresponding to average molecular weights from 80,000 to 1,200,000 Da (Table 7.9).

7.3.1.3 Hydroxyethyl cellulose

HEC is a partially substituted polyhydroxyethyl ether of cellulose (Fig. 7.45).

It is used in ophthalmic and topical formulations as a viscosity-modifying agent and as a binder, controlled-release matrix former, and as a film-coating

agent in solid dosage forms. Similar to the synthesis of HPC, each of the added hydroxyethyl group introduces a secondary hydroxyl group that can be further etherified during the preparation of HEC, giving rise to an additional chain extension. In this case, the number of moles of hydroxyethyl groups per anhydroglucose ring, the molar substitution MS, will be higher than the degree of substitution DS. A typical structure of HEC with substitution sites on the anhydroglucose rings, giving rise to MS value of 2.5 and DS value of 1.75, is illustrated in Fig. 7.40. HEC dissolves quickly in water (hot or cold) to form a clear and smooth solution, which does not gel or precipitate even when heated to the boiling point of water. HEC is available commercially in several grades that vary in viscosity and DS, corresponding to average molecular weights from about 90,000 to 1,300,000 Da (Table 7.9).

7.3.1.4 Ethyl cellulose

Ethyl cellulose (EC) is a partly *O*-ethylated cellulose ether derivative (Fig. 7.46).

It is insoluble in water but soluble in a variety of solvents. EC is widely used in oral pharmaceutical formulations as a coating agent for tablets and granules to regulate the drug-release rate and to mask unpleasant taste, as well as in microencapsulation and in

matrix tablets to achieve modified release. EC films can be applied from organic solvent systems, but this has largely been replaced by the use of a more environmentally friendly aqueous dispersion of EC without the need for organic solvents.^{68–71} The substitution level or the ethoxyl content directly impacts the properties of the resulting EC. A typical structure of EC with a DS value of 2.5 corresponding to a 48.5 wt.% ethoxyl content is shown in Fig. 7.46. If the DS of EC is increased to 2.8, a largely insoluble material would result, underscoring the interplay of solid-state packing defects in modulating the solubility of cellulose derivatives. Currently, USP-NF and EP define the ethoxyl content of EC to be between 44.0 and 51.0 wt.%. EC is available commercially in several types that vary in viscosity and ethoxyl content, corresponding to average molecular weights from about 65,000 to 215,000 Da; the most widely used is the standard or *N* type that has 48.0–49.5 wt.% ethoxyl content (Table 7.9). EC can also be used as a binder/matrix former for matrix tablet formulations for modified-release applications.⁷²

7.3.1.5 Methyl cellulose

Methyl cellulose (MC) is a methyl ester of cellulose (Fig. 7.47) that contains 27.5–31.5% of the methoxy groups. A typical structure of MC with DS value of

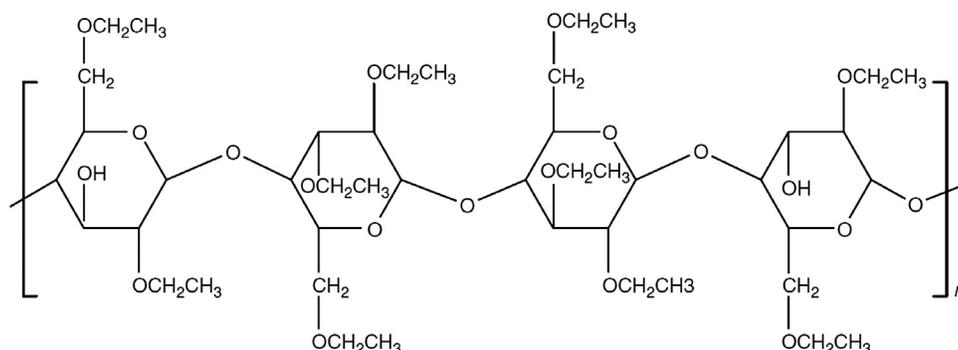


FIGURE 7.46 Typical structure for ethyl cellulose with a net degree of substitution of 2.5. This corresponds to a wt.% ethoxyl of 48.5, which is representative of an *N* or standard grade of this material. If the net DS of the ethyl cellulose is substantially increased to the order of 2.8, a largely insoluble material results, underscoring the interplay of solid-state packing defects in modulating cellulose derivative solubility.

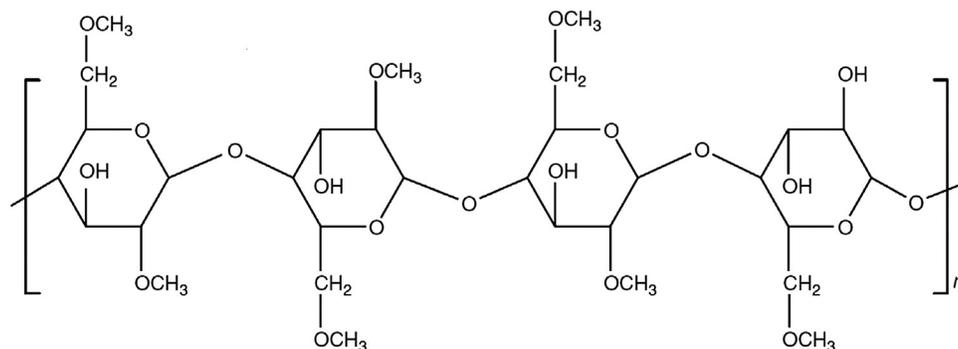


FIGURE 7.47 Typical structure for methyl cellulose with a net degree of substitution of 1.75, which corresponds to a wt.% methoxyl level of 29.1.

1.75 corresponding to 29.1 wt.% methoxyl content is shown in Fig. 7.47. MC is soluble in water, and its aqueous solution exhibits thermal gelation properties. A wide range of viscosity grades (5–75,000 cP at 2%) corresponding to average molecular weight range of 10,000–220,000 Da are available commercially. MC is widely used in oral solid pharmaceutical formulations as a binder, a coating agent, and a disintegrant for tablets, as well as in matrix tablets to achieve sustained release.

7.3.1.6 Sodium carboxymethyl cellulose

Sodium carboxymethyl cellulose (NaCMC) is the sodium salt of the carboxymethyl ether of cellulose, an anionic derivative (Fig. 7.5).

It is widely used in oral, ophthalmic, injectable, and topical pharmaceutical formulations, primarily for its viscosity-increasing and gelling properties. For solid dosage forms, it is mostly used as a binder or matrix former. Pharmaceutical grades of NaCMC are available commercially at DS values of 0.7 and 0.9, with a corresponding sodium content of 6.5–9.5 wt.% (USP/EP), and at a DS value of 1.2 with sodium content of 10.4–12 wt.% (USP). NaCMC is highly soluble in water at all temperatures, forming clear solutions with viscosities depending on the substitution grade and concentration. NaCMC is available in several different viscosity grades, corresponding to average molecular weights from about 49,000 to 725,000 Da (Table 7.9).

7.3.1.7 Cellulose acetate

Cellulose acetate (CA) is cellulose with its hydroxyl groups partially or completely acetylated (Fig. 7.48).

It is insoluble in water but soluble in a variety of organic solvents. CA is available in a wide range of acetyl contents (29.0–44.8%) and chain lengths, with molecular weights ranging from 30,000 to 60,000. CA is widely used in pharmaceutical formulations as semipermeable coatings on osmotic tablets to regulate the osmotic water influx, thereby controlling the drug-release rates.^{73–76} With appropriate additives, it is also used as coatings on

tablets or granules or as shell material for microcapsules to achieve controlled drug release, or as coatings on tablets or granules for taste-masking purposes. CA can also be employed to formulate matrix tablet prepared by direct compression.

7.3.1.8 Cellulose derivatives with pH-dependent solubility

HPMCAS (Fig. 7.49) is produced by the esterification of HPMC with acetic anhydride and succinic anhydride in a reaction medium of a carboxylic acid, such as acetic acid, and using an alkali carboxylate, such as sodium acetate, as catalyst.

HPMCAS retains the structure diversity of the starting material HPMC where the added hydroxypropyl group introduces a secondary hydroxyl group, which can also be etherified during the preparation of HPMC, giving rise to an additional chain extension. It is available in several grades with varying extent of substitution, mainly of acetyl (2.0–16.0%) and succinoyl (4.0–28.0%) groups with molecular weights ranging from 55,000 to 93,000 Da. HPMCAS is insoluble in gastric fluid but starts to swell and dissolve at a pH above 5 depending on the extent of substitution. The dissolution pH increases as the ratio of acetyl over succinoyl substitution increases. Traditionally, HPMCAS has been used in enteric film coating of tablets and multiparticulates.⁷⁷ For aqueous film-coating formulations, a dispersion of HPMCAS fine powder and triethyl citrate (as a plasticizer) in water is commonly utilized. Organic solvents can also be used as vehicles for applying this polymer as a film coating. However, today HPMCAS is the most widely utilized amorphous solid dispersion polymer for drug solubilization. It is most easily used via spray drying, but hot-melt extrusion is also becoming increasingly common.^{78,79}

Cellulose acetate phthalate (CAP) (Fig. 7.50) is a product of esterification of cellulose acetate (CA) with phthalic anhydride in the presence of a tertiary organic base such as pyridine or a strong acid such as sulfuric acid containing 21.5–26.0% of acetyl groups

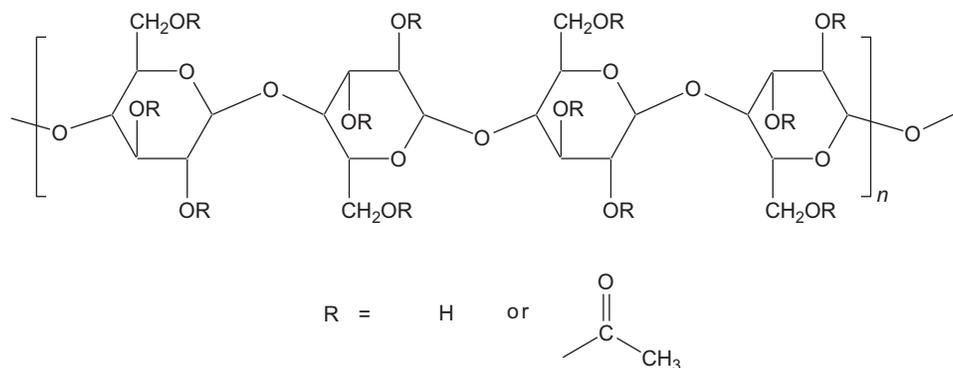


FIGURE 7.48 Typical structure for cellulose acetate (CA).

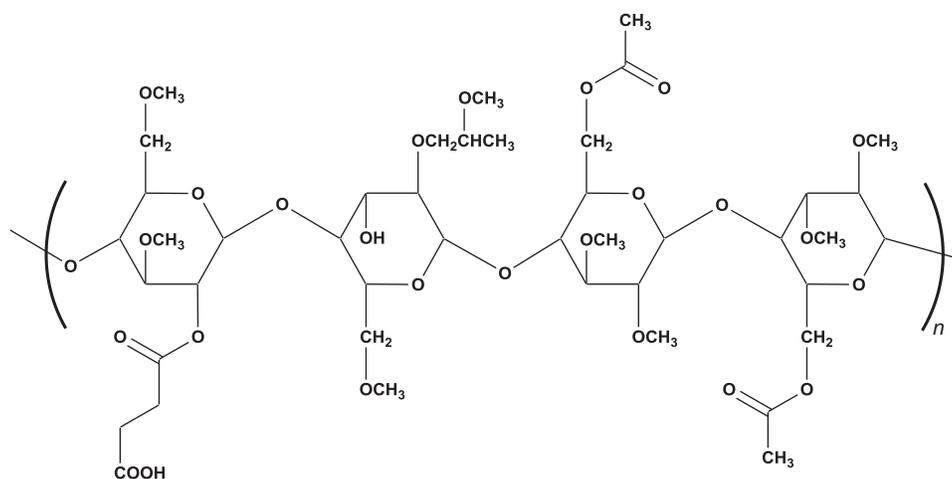


FIGURE 7.49 Typical structure for hydroxypropyl methylcellulose acetate succinate (HPMCAS).

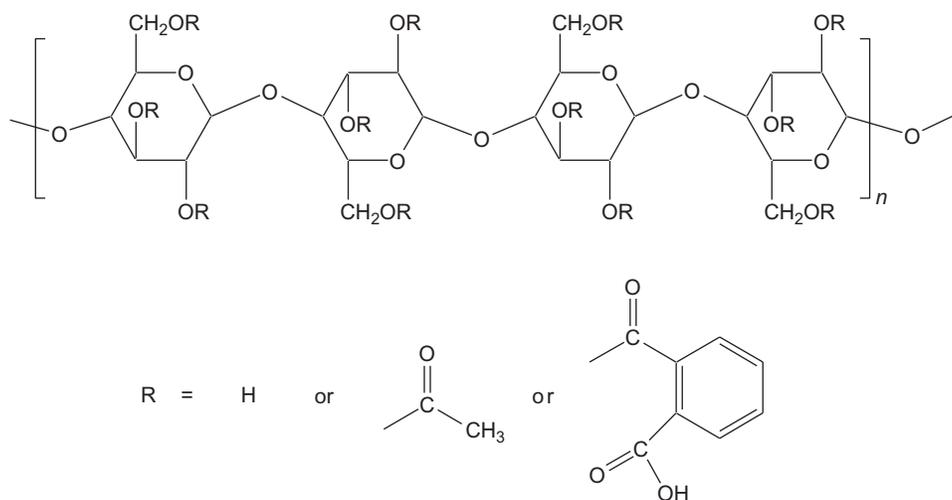


FIGURE 7.50 Typical structure for cellulose acetate phthalate (CAP).

and 30.0–36.0% of phthalyl groups with a viscosity (15% in acetone) ranging from 50 to 90 cP.

CAP has pH-dependent solubility and is soluble in aqueous solutions at a pH above 6. CAP is mainly used as an enteric film-coating material or as a matrix binder for tablets and capsules. It provides protection of API in the strongly acidic gastric fluid, but it dissolves in mildly acidic or neutral intestinal environment to make the drug available for absorption. CAP is commonly applied to solid-dosage forms either by coating from an aqueous dispersion or a solution of organic solvent or by direct compression.

7.3.2 Synthetic polymers

7.3.2.1 Acrylic acid polymers

Synthetic polymers based on acrylic, especially methacrylic acids, have found extensive applications in the oral solid formulations to protect the active

ingredients as versatile film former for coatings or to release the drug in a controlled manner as a matrix former or a diffusion barrier for a reservoir system.

Such polymers can be made as cationic, anionic, and neutral (nonionic) polymers.

7.3.2.1.1 Polyacrylic acid (carbomer; carbopol)

Carbomers (Fig. 7.51) are synthetic high-molecular-weight polyacrylic acids cross-linked with allyl sucrose or allyl pentaerythritol and contain between 56 and 68% w/w carboxylic acid groups. The molecular weight of carbomer is estimated to be at 7×10^5 to 4×10^9 Da. As three-dimensionally cross-linked microgels, carbomers do not dissolve but swell to a remarkable extent in water after neutralization to form a gel.⁸⁰ Carbomers are used in liquid or semisolid pharmaceutical formulations as rheology modifiers. Carbomers having low residual solvent content, such as Carbopol 971P NF or

Carbopol 974P NF, may be used in oral solid dosage forms as binders or matrix tablet formers.^{81–84}

7.3.2.1.2 Polymethacrylate

Polymethacrylates (Fig. 7.52) are synthetic linear copolymers prepared by free-radical polymerization. They may exist as cationic, anionic, and neutral (nonionic) polymers depending on the starting

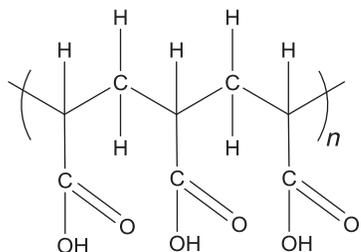
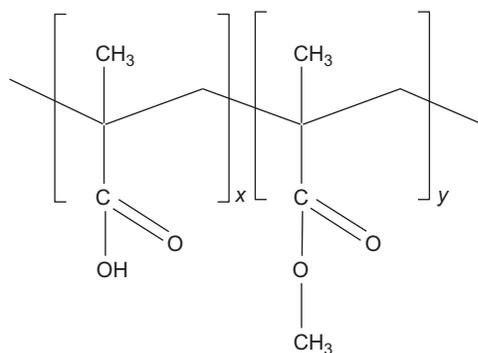


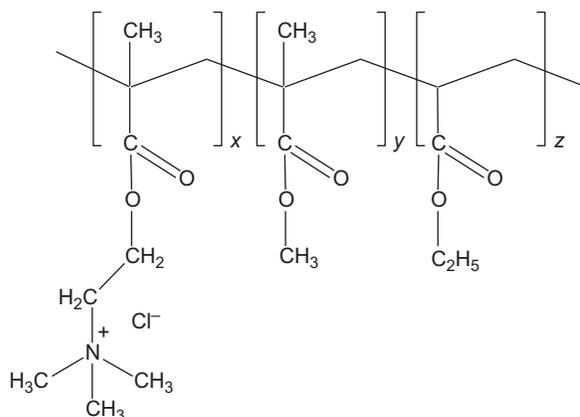
FIGURE 7.51 Typical structure for carbomers.

monomers for preparing the polymers. The functionality and applications of such polymers depend on the structures and ionic charges of the polymers.^{85–88}

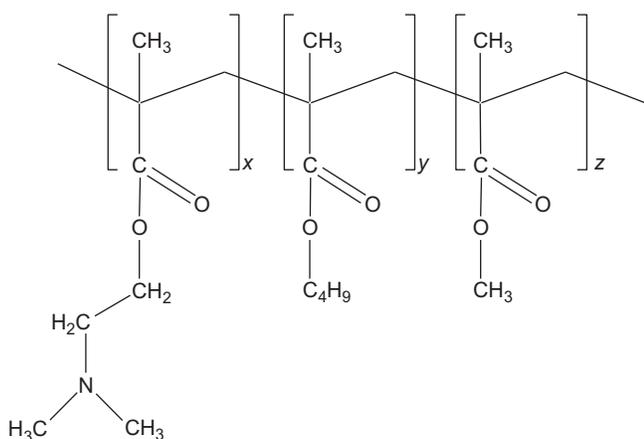
Anionic polymers: Anionic polymethacrylate polymers contain methacrylic acid functional groups, which dissociate and render the polymer soluble at the higher pH of the small intestine and colon. Anionic polymers containing methacrylic acid–ethyl acrylate copolymer (1:1) in coating products (eg, Eudragit[®] L 30-D or Kollicoat[®] MAE 30 DP) are soluble from a pH 5.5 but insoluble at the low pH in the stomach. Such polymers offer enteric protection to many active ingredients in oral solid formulations in the gastric environment and trigger drug release at a selected pH for targeted drug delivery in the GI tract. Anionic copolymers of methacrylic acid and methyl methacrylate at a ratio of approximately 1:1 (Type A; eg, Eudragit L) and approximately 1:2 (Type B; eg, in Eudragit S). Both polymers are readily soluble in neutral to weakly alkaline conditions (from pH 6 for



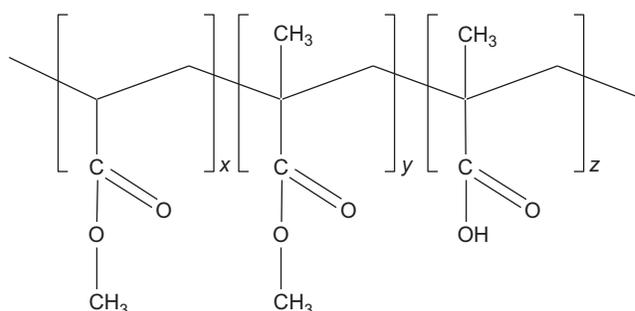
Methacrylic acid–methyl methacrylate copolymer (1:1 or 1:2)



Poly(ethylacrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) (1:2:0.2 or 1:2:0.1)



Poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) (1:2:1)



Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) (7:3:1)

FIGURE 7.52 Typical structure for polymethacrylates.

Type A and from pH 7 for Type B); the latter enables drug delivery to the colon, since the polymers becomes soluble at pH >7.0.

Cationic polymers: Cationic polymethacrylate polymers typically consist of copolymers of ethyl acrylate, methyl methacrylate, and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts, which increase the polymer swelling in aqueous media, thereby making the polymers more permeable. Cationic polymethacrylate containing more quaternary ammonium groups (eg, Eudragit RL 100) is, therefore, more permeable than the one containing less quaternary ammonium groups (eg, Eudragit RS 100) as a consequence. Both polymethacrylate polymers are commercially available as a fine powder (eg, Eudragit RS PO), a solution in organic solvents (eg, Eudragit RS 12.5), or an aqueous dispersion (eg, Eudragit RS 30 D). Both polymethacrylate polymers can be mixed in any ratio to modulate the drug-release rate in addition to well-known strategies of varying coating thickness and incorporation of pore formers.

Another available cationic polymethacrylate is a copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate (eg, Eudragit E 100). It is soluble in gastric fluid below pH 5 but becomes swellable and permeable, but not soluble, above pH 5. This cationic polymethacrylate can be used for taste-masking applications.

Neutral polymers: Neutral polymethacrylates based on copolymers of ethyl acrylate and methyl methacrylate (2:1) do not contain ionic groups and, therefore, only swell in aqueous media independently of pH without dissolving. These are generally available as aqueous dispersions with a solid content at 30% and 40% respectively (eg, Eudragit NE 30 D and Eudragit NE 40 D). Films prepared from these are insoluble in water but will swell and become permeable when they are in contact with water and exhibit pH-independent drug permeability. Such neutral polymethacrylate aqueous dispersions can be used for controlled-release coatings and wet-granulation binders.

7.3.2.2 Polyvinylpyrrolidone

7.3.2.2.1 Povidone

Povidone (Fig. 7.53) is a linear polymer of 1-vinyl-2-pyrrolidinone monomer with different degrees of

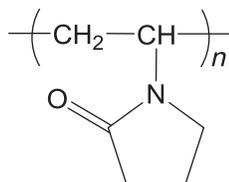


FIGURE 7.53 Chemical structure for polyvinylpyrrolidone (PVP).

polymerization, which results in polymers of a wide range of molecular weights (2,500–3,000,000 Da).

Povidone is water soluble, with the maximum concentration being limited only by the solution viscosity. Being nonionic, the viscosity of povidone in an aqueous solution is unaffected by the pH or salt concentration. Povidone is widely used in solid-dosage forms. In tablet formulations, povidone solution is used as wet-granulation binder. Povidone can also be incorporated to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone may be used as a dissolution-enhancing agent in oral formulations for poorly soluble drugs involving processes such as spray drying and hot-melt extrusion.^{79,89} Povidone is a well-known complexing agent; for example, the ability to complex with iodine is of particular commercial importance, providing an antibacterial povidone iodine solution and powder that are widely used in medical and hospital settings. Povidone solutions may also be used as a film former for coating formulations or as binders for drug layering onto a substrate such as sugar or microcrystalline cellulose beads. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of oral suspensions and solutions. Increasingly due to its advantageous solubility in PEG 400 and glycerin, povidone is also used as a viscosifying and stabilizing agent in liquid-filled gelatin capsules.

7.3.2.2.2 Crospovidone

The preparation of vinylpyrrolidone for crospovidone is similar to povidone. The vinylpyrrolidone is polymerized in solution using a catalyst to produce crospovidone by a popcorn polymerization process. Crospovidone is a white, free-flowing, practically tasteless and odorless, hygroscopic powder.

Crospovidone is a cross-linked, water-insoluble superdisintegrant. It is usually incorporated dry in the running powder of a tablet formulation, but it can also be processed by wet and dry granulation methods. Typical use levels in tablet formulations range from 2% to 5%, but in orally disintegrating tablets in particular and some capsule formulations, crospovidone is used at much higher levels up to 30%. Similar to sodium starch glycolate, crospovidone disintegrates tablets mainly by swelling, with little tendency to form gels. Crospovidone can also be used for solubility enhancement of poorly soluble drugs in the process of coevaporation. This process enables the drug adsorption onto crospovidone in the presence of a suitable solvent, and the solvent is then evaporated to provide a solid mixture with a faster drug dissolution rate.

7.3.2.3 Polyvinyl alcohol (PVA)

Polyvinyl alcohol (PVA) is produced through the hydrolysis of polyvinyl acetate. The repeating unit of vinyl alcohol is not used as the starting material because it is unstable and cannot be isolated. The hydrolysis of polyvinyl acetate proceeds rapidly in methanol, ethanol, or a mixture of alcohol and methyl acetate, using alkalis or mineral acids as catalysts.

PVA occurs as an odorless, white to cream-colored granular powder. It is a linear water-soluble polymer represented by the formula $(C_2H_4O)_n$ (see structure in Fig. 7.54). The value of n for commercially available PVA is between 500 and 5000, equivalent to a molecular weight range of 20,000–200,000. Various grades of PVA are commercially available. The DP and the degree of hydrolysis are the two key factors affecting their physical properties. Typically, pharmaceutical grades are partially hydrolyzed materials.⁶⁵

The predominant commercial use of polyvinyl alcohol in solid oral dosage forms is as an immediate-release, film-coating polymer. It is also used as a viscosity-enhancing agent in ophthalmic and topical formulations.

7.3.2.4 Polyethylene oxide (PEO) and polyethylene glycol (PEG)

Polyethylene oxide (PEO) and polyethylene glycol (PEG) have the same CAS registry number 25322-68. Both PEO and PEG are nonionic homopolymers of ethylene oxide, sharing the same formula $(CH_2CH_2O)_n$ (Fig. 7.55) where n represents the average number of oxyethylene groups, with $n = 5–182$ for typical PEGs (avg. MW 200-8000) and much larger n 's for PEOs (avg. MW 100,000 up to several million).

7.3.2.4.1 Polyethylene glycol (PEG)

Polyethylene glycol (PEG) is formed by the reaction of ethylene oxide and water under pressure in the presence of a catalyst.

PEG is soluble in water and miscible in all proportions with any other grade of PEG (after melting, if

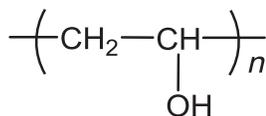


FIGURE 7.54 Chemical structure for polyvinyl alcohol (PVA).

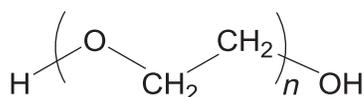


FIGURE 7.55 Chemical structure for polyethylene glycol (PEG) and polyethylene oxide (PEO).

necessary). Liquid PEGs are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid PEGs are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether but insoluble in fats, fixed oils, and mineral oil. Aqueous solutions of higher-molecular-weight grades may form gels.

In tablet formulations, PEGs of a high molecular weight can enhance the effectiveness of tablet binders and impart plasticity to granules when it is used in conjunction with another binder. PEG may prolong disintegration if used above 5% w/w. Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression.

In coating formulations, low-molecular-weight PEG is mainly used as a plasticizer. Higher molecular weights can be useful as hydrophilic polishing materials. Solid PEGs are also used to enhance the ductility of the coating membrane and avoid rupture of the coating film when the coated microcapsules are compressed into tablets. The presence of PEGs in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films.⁶⁵

PEGs may also be used to enhance the aqueous solubility of poorly soluble drugs by making solid dispersions with an appropriate grade of polyethylene glycol by either spray drying or hot-melt extrusion.

Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents. Polyethylene glycol has also been used in insulin-loaded microparticles for the oral delivery of insulin; it has been used in inhalation preparations to improve aerosolization.

7.3.2.4.2 Polyethylene oxide (PEO)

Polyethylene oxide (PEO) is prepared by the polymerization of ethylene oxide with the use of a suitable catalyst.

PEO is soluble in water and some commonly used organic solvents such as acetonitrile, chloroform, and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols. It may contain up to 3% of silicon dioxide or suitable antioxidant.

Higher-molecular-weight PEO is predominantly used in extended-release formulations as a hydrophilic matrix former at levels ranging from 5% to 75%. PEO can be used as a tablet-and-extrudate forming material or an aid in hot-melt extrusion. The relationship between the swelling capacity and the molecular

weight is a good guide when selecting products for use in immediate- or sustained-release matrix formulations. Polyethylene oxide has also been shown to have mucoadhesive properties. PEO films exhibit good lubricity under wet conditions.⁶⁵

PEOs are an effective viscosity enhancer at low-use level, although alcohol is usually added to water-based formulations to provide improved viscosity stability.

7.3.2.5 Ion-exchange resins

Ion-exchange resins are generally made from methacrylic acid, sulfonated styrene, and divinylbenzene (DVB). A generic structure of such cation-exchange resin is shown in Fig. 7.56.

Cation exchangers are anionic polymers that contain carboxyl or sulfate groups with hydrogen, potassium, and sodium as counterions. Cation exchangers with weak acidity are made from a polymer of methacrylic acid (containing COOH) cross-linked by DVB. The counterion of the acidic carboxyl group is either hydrogen (as in polacrilex resin) or potassium (as in polacrilin potassium). To make a cation-exchange resin with a stronger acidity, water-insoluble styrene is used to prepare the polymer, which is sulfonated to make it hydrophilic. DVB is also used to cross-link the polymer, and the counterion of the sulfate group (SO₃) is generally sodium.

Ion-exchange resins swell in an aqueous medium. The DVB-cross-linked potassium methacrylate copolymer possesses such a high swelling capacity that it is used as a disintegrant for oral solid formulations.

Ion-exchange resins have fixed ionic functional groups that can provide binding of ionic drugs. Release of the bound drugs requires an exchange with counterions such as hydrogen or sodium, which are

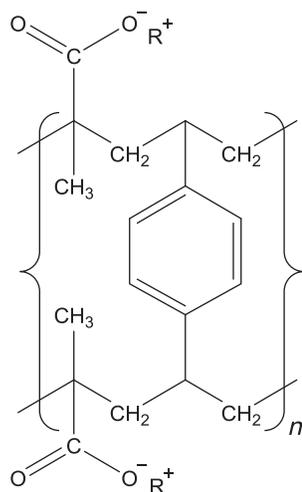


FIGURE 7.56 Generic structure of a cation-exchange resin based on polymethacrylic acid, where R = hydrogen for polacrilex resin, R = potassium (partial) for polacrilin potassium.

available in the gastrointestinal tract. Because of their unique properties, the ion-exchange resins are generally used for taste masking, drug stabilization, and sustained-release applications or a zero-order release due to their high swelling capacity.^{90,91}

The commercial product of sodium polystyrene sulfonate (Amberlite™ IRP69) is used to treat hyperkalemia. On the other hand, cationic ion-exchange resins with the ability to exchange anions carry quaternary ammonium groups, $-N^+(R)_3$ with chlorine as a counterion. Cholestyramine resin (Duolite™ AP143) is cationic styrene DVB polymer that is an anion exchanger and is used to reduce cholesterol or to sequester the bile acid.

7.4 CONCLUSION

In many respects, polymeric materials have a preeminent position among excipients, as they form the backbone of modern pharmaceutical practice and drug-delivery technologies in particular. With the exception of a few technologies, the majority of bioavailability enhancement, modified-release, and controlled-release technologies rely on the unique properties of polymers to achieve drug-release control through a variety of mechanisms. These may include dissolved drug diffusion through water-insoluble, polymeric film coatings or diffusion and erosion from water-soluble, hydrogel-forming polymeric systems. Some of the obvious, inherent properties of polymers that continue to enable the development of new technologies include their large molecular weight, which facilitates entanglement and network formation, thus allowing diffusion control. Also important is the availability of large numbers of different polymers, which are generally regarded as safe and which have good processing and manufacturing properties such as solubility in aqueous systems and common nonaqueous solvents, good stability, good plastic deformation and compaction properties, and excellent film-forming properties.

As highlighted in this chapter, the key to understanding and productively using polymeric materials in solid dosage form design and general industrial practice is to appreciate their unique properties as compared to well-defined, discrete small molecules. In particular, unlike small molecules with a well-defined and discrete structure, state, and properties, polymers are best viewed in terms of a continuum and distribution of structural and physical property characteristics and states. Furthermore, while structure-property relationships are frequently complex and multifactorial, we hope to have conveyed that even with the application of only a small set of relatively simple rules and principles, it is possible to make

more rational and science-based decisions with regard to polymer selection to achieve the desired effects and robust systems. This is particularly important in the context of the current industry focus on QbD and the fact that polymeric materials frequently comprise a significantly greater proportion of the modern dosage form than does the drug. Looking to the future, it is clear that polymers will continue to be a tool in the development of solid oral dosage forms.

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