How Does a Timed-Release Medicine Work?

The formulation of timed-release medicines is based on the specific response of polymeric coatings to their chemical environment. The chemical packaging of these medicines determines the precise conditions for effective control and sustained dosage of these drugs.

The Chemical Basics

Physicians utilize a variety of protocols and therapies to heal and cure patients. Some medical treatments require the sustained application of a drug for maximum effectiveness. When hospitalized, a patient can receive this continued drug delivery through an intravenous (IV) unit. Some oral medications are chemically formulated to achieve this same effect. A medicine taken orally can often be gradually released in the body over a specified time interval by carefully designing the coating that encapsulates the medication. For example, the decongestant Contac contains numerous tiny beads of medicine that are covered by a water-soluble polymeric coating of varying thickness. The thicker the coating, the longer the time required for the coating to dissolve in water and the slower the release of the medicine. The claim of an effective “twelve-hour medicine” is based on the precise combination of beads of medicine with prescribed thicknesses of polymeric coating to sustain the controlled release for an extended period of time. Thin coatings obviously dissolve quickly, while thicker layers take longer (up to 12 hours, in this case). Timed-release formulations using “microencapsulation technology” are also used for agricultural purposes (e.g., fertilizers) and insect control (e.g., a six-month pest control).

The Chemical Details

FMC designs one such water-soluble coating for timed-release medications — Aquacoat ECD, a 30% by weight aqueous dispersion of ethylcellulose. This polymer is used to coat drug-layered beads that are delivered using gelatin capsules.
for a pH-independent sustained release. Cellulose is a natural polymer containing repeating glucose units (monomers). Cellulose forms during a condensation polymerization reaction (Fig. 14.1.1) in which each new link of glucose monomers releases a water molecule. The -OH and -CH₂OH substituents on the glucose rings are replaced with -OCH₂CH₃ and -CH₂OCH₂CH₃ groups in ethylcellulose (Fig. 14.1.2).

Some extended-release preparations are designed with a coating that responds to the acidity of its environment. The polymeric coating of the medicine is formulated for stability during oral delivery and for eventual solubility at the intended organ. The contrasting acidic content of the stomach and the more basic environment of the intestines enable these formulations to function. For example, hydroxypropyl methylcellulose phthalate (HPMCP) (Fig. 14.1.3) is an enteric (i.e., solubilized in the intestinal tract) coating designed to protect acid-sensitive
drugs from being destroyed by gastric acid in the stomach. In a more alkaline environment, deprotonation of the –COOH carboxyl groups (to form –COO–carboxylate functionalities) is believed to enable the dissolution of the polymeric HPMCP, thereby releasing the encapsulated drug. [1] Enteric coating materials are specifically used to target timed-release medications to treat colon inflammations or other disorders of the digestive tract. In addition, enteric coatings are placed on aspirin caplets designed for the temporary relief of arthritic and rheumatic pain, muscle aches, joint pain, and back pain. The coating allows the caplet to pass through the stomach to the intestine before it dissolves, to help prevent stomach irritation.

Polymer coatings responsive to temperature or moisture form the basis for medications delivered transdermally using patches on the skin or internally via inserts implanted in the body. Oral nitroglycerin (Fig. 14.1.4) tablets to prevent angina attacks or scopolamine (Fig. 14.1.5) to protect against motion sickness are two examples of drugs that can penetrate the skin and flow into the bloodstream at a rate dictated by a rate-controlling membrane in the patch. Hydrolysis of nitroglycerin leads to the formation of the reactive free radical nitric oxide, NO. NO activates guanylate cyclase to produce cyclic guanosine monophosphate (cGMP); cyclic GMP decreases cellular calcium levels, thereby causing dilation or expansion of the blood vessels to reduce myocardial oxygen demand. [2] Dilation of the arteries increases blood flow to the heart and relieves the chest pains that result from an insufficient supply of oxygen to the heart muscle. The sophistication of the technology of timed-release medications arises from the extensive structural
control that the chemist has available for the design of polymeric coatings and matrices.

**KEY TERMS:** polymer microencapsulation enteric

**References**


**Related Web Sites**


### 14.2 How Does “Scratch & Sniff” and Carbonless Copy Paper Work?

The clever combination of chemistry and microsphere technology enables advertisers to take advantage of the incredible marketing power of scent. These innovations have also modernized paper-based recordkeeping and business transactions.

**The Chemical Basics**

These two seemingly dissimilar applications have a common basis—both are examples of the pressure-sensitive release of a chemical. How are these products designed? Tiny spherical capsules (*microcapsules* or *microspheres*) with a glass or polymer shell are filled with a liquid core and glued onto paper. For a “scratch-and-sniff” ad, the core of the microcapsules contains a liquid with the desired scent; for carbonless paper, a liquid ink or dye is encapsulated within the
Microspheres that adhere to the underside of the paper. When the paper ad is scratched, the shell of the microsphere is broken. By exposing the liquid cavity, the scent of the enclosed perfume or fragrance is easily detected. Similarly, when pressure is applied to the copy paper through a pen or typewriter, the encapsulated colorless dye is released and reacts with an acidic chemical on the paper underneath to darken and transfer ink to the underlying paper.

Microencapsulation is the term for the shielding of solid, liquid, or gaseous active ingredients by enclosure of the active component within a protective shell. To release the contents of the microcapsule, four techniques are often employed. Scratch-and-sniff cards and carbonless copy paper rely on the mechanical rupture of the microsphere shell induced by pressure. Timed-release medicines and agrochemicals are often based on water-soluble polymeric coatings that dissolve over time. (See Question 14.1.) Sustained release of medications is also achieved via diffusion of the active components through microcapsule walls. Thermal breakdown or melting of a solid microcapsule wall by increased temperature is also a release mechanism, used to liberate fat-encapsulated baking soda in packaged baking mixes, for example.

The Chemical Details

The polymer and glass microspheres employed in the pressure-sensitive release of chemicals range in size from 1 μm to 1 mm in diameter. (For comparison, a human hair is typically 80-100 μm in diameter.)[1] A scanning electron micrograph illustrating the morphology of the particles appears in color Fig. 14.2.1.[2]

A variety of techniques are employed to achieve microencapsulation. One of the earliest methods, developed in the 1930s, is known as coacervation or phase separation. This method reproducibly applies a uniform, thin, polymeric coating to small particles of solids or to droplets of pure liquids and solutions. To apply this method, four components are necessary: the material to be coated (core), a wall-forming polymer, a suitable solvent (liquid-manufacturing vehicle), and a coacervation (phase-separation) inducer.[3] For water-soluble core materials, a polymer soluble in a nonpolar solvent such as cyclohexane must be chosen (e.g., ethylcellulose). For core substances not miscible in water, a water-soluble polymer (e.g., gelatin) is required. The polymer must also be chemically compatible with the core material and be capable of forming a cohesive film on the core surface. Selection of an appropriate polymer, whether natural or synthetic, should also address the needs for a coating material with the requisite strength, flexibility, impermeability, and stability.

In the coacervation process, the core substance is first added to a homogeneous solution of the selected solvent and polymer. Mechanical agitation is used to disperse the immiscible core to create tiny droplets suspended in solution (i.e., an emulsion). The coacervation or phase separation phenomenon is then induced by several means, such as changing the temperature and/or acidity of the polymer solution or adding salts, nonsolvents, or incompatible (immiscible) polymers to
the polymer solution. For example, by adjusting the acidity of the system through the addition of an acid, a phase separation may be induced. In other words, two immiscible liquid phases are created with different amounts of the solubilized polymer in each phase. The supernatant phase has low polymer concentrations, while the coacervate phase has a relatively high concentration of the polymers. The polymer is selected so that the coacervate phase preferentially adsorbs onto the surface of the dispersed droplets to form the shell of the microcapsules. Once the fluid film of polymer is deposited from the coacervate onto the core, the shell must be solidified. Cooling and further chemical reaction with a cross-linking agent such as formaldehyde hardens the microcapsule walls. The microcapsules are then separated by settling or filtration, and then washed, filtered, and dried.

KEY TERMS: microencapsulation microsphere

References


Related Web Sites


- Microencapsulation, Faculty of Pharmaceutical Sciences, Chulalongkorn University, http://www.pharm.chula.ac.th/microcap/MIC.HTM

How Do “Repositional Self-Adhesive Paper Notepad Sheets” (Post-it Notes) Work?

Post-It Notes are ubiquitous forms of communication at the office, in schools, and at home. This extremely useful invention is actually the result of a failed experiment. How does chemistry contribute to the function of this convenient product?

The Chemical Basics

Office supplies and office communication have been revolutionized by the introduction of the 3M product Post-it Notes in 1980. The temporary adhesive of these self-sticking notes actually was initially rejected as a glue by its inventor, 3M chemist Spencer Silver, because of its impermanence. However, 3M researcher Art Fry found a niche for the adhesive — as an adhesive for a temporary bookmark for his choir hymnal.\[1\] Key to the performance of these removable, repositional adhesive products is the application of the adhesive to the backing of a note sheet via tiny microspheres rather than a continuous film. With an average particle diameter of 25–45 µm, the microsphere adhesives form a discontinuous layer that assists in retaining the ability to re-apply the note to new surfaces. Traditional adhesive tape contains particles of smaller dimension (typically 0.1 to 2.0 µm) that coalesce to form a continuous film that limits removal.\[2\]

The Chemical Details

The tacky polymeric microspheres that comprise the pressure-sensitive adhesive layers of “repositionable notes” are patented inventions. One such material (U.S. Patent 5,714,237)\[3\] is prepared by a free-radical polymerization reaction of iso-octyl acrylate (Fig. 14.3.1) in the presence of polyacrylic acid with a chain-transfer agent (dodecanethiol) (Fig. 14.3.2), an initiator (monomer soluble bis-(t-butylcyclohexyl)peroxycarbonate) (Fig. 14.3.3), and a detergent (ammonium lauryl sulfate) (Fig. 14.3.4). The adhesive polymeric composition is recovered and blended with a solid coating mixture to create the microspheres.

Free-radical polymerization reactions are also known as chain-growth or addition polymerization reactions. Let’s look at a chain-growth polymerization re-
actions in more detail. As the name suggests, these processes convert small monomer molecules to larger polymers by the successive addition of monomer molecules onto the reactive ends of a growing polymer. An initiator is required in chain-growth polymerization reactions. The function of the initiator is to react with the monomer to form another reactive compound, thereby beginning (initiating) the linking process. Under the proper experimental conditions, the peroxycarbonate initiator easily cleaves at its oxygen-oxygen bond to create unstable species called free radicals (or simply radical species) that are characterized by an unpaired electron:

\[ \text{C}_6\text{H}_{11}\text{OC(O)OOC(CH}_3\text{)}_3 \rightarrow \text{C}_6\text{H}_{11}\text{OC(O)O}^- + \cdot \text{OC(CH}_3\text{)}_3. \]

One of these free radicals may decompose further by releasing carbon dioxide and generating a new free radical.

\[ \text{C}_6\text{H}_{11}\text{OC(O)O}^- \rightarrow \text{C}_6\text{H}_{11}\text{O}^- + \cdot \text{CO}_2 (g). \]

These reactive species initiate the linking process by adding to the double bond of the chosen acrylate monomer (isooctyl acrylate) to create another reactive radical species. This linking process may be represented by

\[ \cdot + \text{H}_2\text{C}=$\text{CHX} \rightarrow \text{H}_2\text{C}=$\text{CHI}^- \cdot . \]
This new free radical adds to the double bond of another monomer molecule, growing the polymer chain. The polymerization process ends as the unpaired electrons of two free radicals combine to form a single bond:

\[ \text{R-CH}_2\text{-CHX} \cdot + \cdot \text{CHX-CH}_2\text{-R} \rightarrow \text{R-CH}_2\text{-CHX-CHX-CH}_2\text{-R}. \]

**References**


**Related Web Sites**


- “Free Radical Vinyl Polymerization.” Department of Polymer Science, University of Southern Mississippi, http://www.psrc.usm.edu/macrog/radical.htm


14.4 **What Is “Shatterproof” Glass?**

How does chemistry increase the resistance of glass to impact and shattering?

**The Chemical Basics**

The shatterproof glass used in impact-resistant windows is actually not a glass material derived from silicon dioxide. Instead, shatterproof glass is a *thermoset plastic* or thermoplastic, i.e., a pliable material that is even easier to mold when hot. Shatterproof windows are made using a specific thermoset material known as *polycarbonate* of bisphenol A (or bisphenol A polycarbonate). This clear,
Question 14.4 What Is "Shatterproof" Glass?

The repeating units of the monomer bisphenol A used to construct the polymeric thermoset material used in shatterproof glass.

The glassy polymer is constructed from repeating units of the monomer bisphenol A (Fig. 14.4.1). Thus, bisphenol A polycarbonate is also considered an example of a heterochain polymer, containing atoms in addition to carbon in its backbone chain. Bisphenol A polycarbonate is also a member of the larger polymer family of polyesters, i.e., polymers formed from a large number of smaller molecules, or monomers, by establishment of ester linkages (Fig. 14.4.2) between them.

General Electric markets the polycarbonate of bisphenol A as Lexan. Similar bisphenol A polycarbonate sheets are marketed by Rohm and Haas as the product Tuffak.

The Chemical Details

Polycarbonate is a generic term for the class of polymers consisting of long-chain linear polyesters of carbonic acid, H₂CO₃, and aromatic alcohols known as phenols that possess two hydroxyl groups.

The synthesis of polycarbonate of bisphenol A begins with the reaction of bisphenol A and sodium hydroxide to obtain the sodium salt of bisphenol A, as in Fig. 14.4.3. The sodium salt of bisphenol A is then reacted with phosgene to produce the polycarbonate, as diagrammed in Fig. 14.4.4. Alternative synthesis procedures under exploration replace the solvent phosgene with carbon dioxide to accomplish the final step of the synthesis.
The properties of the polycarbonate of bisphenol A are directly related to the structure of the polymer. The molecular stiffness associated with this polycarbonate arises from the presence of the rigid phenyl groups on the molecular chain or backbone of the polymer and the additional presence of two methyl side groups. The transparency of the material arises from the amorphous (noncrystalline) nature of the polymer. A significant crystalline structure is not observed in the polycarbonate of bisphenol A because intermolecular attractions between phenyl groups of neighboring polymer chains in the melt lead to a lack of flexibility of the chains that deters the development of a crystalline structure.

Another polymer used for unbreakable windows is poly(methyl methacrylate). PMMA is a vinyl polymer, made by free radical vinyl polymerization from the monomer methyl methacrylate, according to the reaction in Fig. 14.4.5.[3] Rohm and Haas introduced this PMMA-based shatterproof glass as Plexiglas.[5]

Imperial Chemical Industries also produces PMMA as Lucite.

**KEY TERMS:** polycarbonate polyester polymer thermoplastic monomer thermoset plastic heterochain polymer
Why Does Superglue Stick to Almost Every Surface?

One commercial adhesive is marketed with the following claims: "High Strength Adhesive," "Durable Bonding," "Fast Acting," "Bonds Metals, Rubber, Ceramics, Plastics, Glass, Wood, Veneers, Fabrics, Vinyl, Cardboard, Cork, Leather, Nylon, and Other Similar Surfaces."[1] How can one substance act as a general purpose adhesive with affinity for so many types of surfaces?

The Chemical Basics

One class of adhesives known as superglues consists of synthetic organic polymers that provide strong and rapid adhesion. These adhesives are unusual in that the polymerization process to form the adhesive occurs upon exposure of the monomer to water. Under most conditions, atmospheric moisture is sufficient to form a strong adhesive. Superglues stick to a variety of surfaces since a film of moisture exists on almost any surface. The quality of bonding will vary with the humidity; the higher the humidity, the better the set.

The Chemical Details

The adhesive marketed under the tradename “Superglue” contains the monomer methyl α-cyanoacrylate (Fig. 14.5.1). A variety of cyanoacrylates are commercially sold as contact adhesives with the alkyl group –R denoted in Fig. 14.5.2 varying from a methyl group to produce ethyl, isopropyl, allyl, butyl, isobutyl,
Figure 14.5.1 ► The monomer methyl α-cyanoacrylate found in the adhesive marketed under the trademark “Superglue.”

Figure 14.5.2 ► The general class of cyanoacrylates with varying alkyl group –R, sold as contact adhesives.

methoxyethyl, and ethoxyethyl cyanoacrylate esters. The properties of the adhesive (e.g., setting time, strength, durability) will vary with the substitution. All of these monomers undergo polymerization in the presence of water. In fact, water serves as an initiator for the polymerization according to an anionic vinyl polymerization mechanism. The overall polymerization process for forming the cyanoacrylate polymer is represented schematically by the reaction in Fig. 14.5.3.

While the formation and subsequent cross-linking of the polymer is one factor in the effectiveness of an adhesive, the adhesive strength of the polymer–surface interface is also critical. Both physical and chemical considerations influence the bonding. A rough or porous surface is generally more effective for “locking” an adhesive to a substrate. However, “chemically active” sites on the surface for promoting interaction via hydrogen bonding, strong dipole–dipole interactions, or other intermolecular attractions also contribute to the adhesion properties.
What Is the Difference between Hard and Soft Contact Lenses?

The number of options for contact lens wearers has been transformed by innovative advances in the chemistry of the polymeric materials used to create these vision products.

The Chemical Basics

Most everyone is familiar with the contrasting resilient, pliable nature of soft contact lenses and the brittle character of hard lenses. Both lenses are constructed from polymers, but the differing chemical composition of each polymer leads to considerably different physical properties.

Hard contact lenses are composed of a polymer that repels water because the constituent repeating units (the monomers that link together to form the polymer) are nonpolar, hydrophobic segments. The first hard contact lens was constructed in 1948 from the monomer known as methyl methacrylate (MMA), yielding the polymer poly(methyl methacrylate) or PMMA. This material offers durability, optical transparency, and acceptable wettability for optimal comfort. Today the rigid lens material of hard contact lenses is often constructed by combining MMA with one or more additional hydrophobic monomers to provide better gas permeability.
The first soft contact lenses were also constructed with a polymeric material containing a single monomeric unit. The added pliability of the soft lens was derived from the more hydrophilic nature of the monomer, enhancing the ability of the polymer to absorb water and provide greater comfort to the lens wearer. This monomer is a derivative of MMA known as hydroxyethyl methacrylate (HEMA). A number of hydrophilic monomers are used in soft lenses today; these materials are referred to as hydrogels because of their ability to absorb significant amounts of water yet remain insoluble.

The soft extended wear lenses popular today are composed of polymers with more than one type of repeating unit, i.e., copolymers. For extended wear a lens with greater oxygen permeability is needed, for the cornea relies on direct oxygen transmission from the atmosphere as a consequence of the lack of blood vessels within the corneal framework. Scientists have found that the higher the water content of a hydrogel polymer, the more extensive the oxygen permeability of the lens formulated from that polymer. A 70% water content is desirable for extended periods of lens wear, expressed as a percentage of the total weight of the polymer. To enhance the water content of these lenses, two basic formulations are employed. In one case a hydrophilic monomer such as HEMA is combined with a highly hydrophilic charged (ionic) monomer. As a consequence of the strong attractive interactions between water and the charged functionality, the water content of the lens is greatly increased, increasing the pliability and comfort level of the lens. Alternatively, the lens can also be designed by combining two highly hydrophilic nonionic monomers.

The Chemical Details

Cross-linked polymeric materials with optical transparency and biocompatibility are used to construct hard contact lenses. The monomers commonly used in hard contact lenses possess a high degree of hydrophobicity due to their inability to form hydrogen bonds with water. The ester methyl methacrylate (MMA) (Fig. 14.6.1), \( \text{CH}_2\text{C(CH}_3\text{)}\text{COOCH}_3 \), was the first monomeric unit used in 1948.

![The molecular structure of the ester methyl methacrylate (MMA).](image)

Lenses with a greater degree of gas permeability were designed in the mid-1970s using siloxane-based monomers. For example, a copolymer of methyl methacrylate and the monomer known as methacryloxypropyl tris(trimethylsiloxy)silane or TRIS (Fig. 14.6.2) was formulated in 1975 to provide a number of desir-
Question 14.6  What Is the Difference between Hard and Soft Contact Lenses? 223

Figure 14.6.2  The molecular structure of the monomer methacryloxypropyl tris(trimethylsiloxy silane) or TRIS.

Figure 14.6.3  The molecular structure of the monomer hexafluoroisopropylmethacrylate (HFIM).

able features such as oxygen permeability, wettability, and scratch resistance. In the 1980s approaches using a number of fluorine-based monomers were successful. A polymer of MMA, TRIS, and hexafluoroisopropylmethacrylate (HFIM) (Fig. 14.6.3) is one such formulation for hard lenses. The hydrogel poly(hydroxyethyl methacrylate) composed of cross-linked monomers of 2-hydroxyethyl methacrylate (HEMA) (Fig. 14.6.4) was the first soft lens material. (Cross-linking consists of bonding between the main polymer chains to add strength to the material.) The presence of the hydroxy functional group (i.e., \(-\text{OH}\)) permits hydrogen bond formation with water and leads to the capacity to absorb water (typi-
Highly hydrophilic nonionic monomers used in hydrogel lenses include glycerol methacrylate (GM) or 2,3-dihydroxypropylmethacrylate (Fig. 14.6.5), N-vinyl-2-pyrrolidinone (NVP) (Fig. 14.6.6), and N,N-dimethylacrylamide (DMA) (Fig. 14.6.7). The Accuvue lens currently manufactured by Johnson and Johnson is an example of a hydrogel polymer with an ionizable monomer (hence enhanced water absorption). Cross-linking HEMA (Fig. 14.6.4) and methacrylic acid (MAA) (Fig. 14.6.8) leads to a water content of 58%. Other combinations of polymers (such as methyl methacrylate and polyvinyl pyrrolidone) lead to soft hydrophilic lens materials with water contents as high as 70%.\(^\text{[3, 4]}\)
What Is the Difference between Hard and Soft Contact Lenses?

**KEY TERMS:** hydrophobic, hydrophilic, monomer, cross-linking

References


Related Web Sites

- “Contact Lenses Identified by Type of Material.” CIBA Vision, http://www.cibavision.com/text/forsight/allabout/C04.03.05.html

Other Questions to Consider

7.6 How is a fabric made water-repellent or waterproof? *See* p. 89.

7.7 How does a bullet-proof vest work? How is it made? *See* p. 92.

7.8 Why is cotton so absorbent and why does it dry so slowly? *See* p. 95.

9.5 Why are floor waxes removable with ammonia cleansers? *See* p. 124.

12.6 What is the purpose of the thread that runs vertically through the clear field on the face side of U.S. currency? *See* p. 152.

13.1 How do sutures dissolve? *See* p. 166.