Chapter-01

ROLE OF POLYMER IN DRUG DELIVERY SYSTEMS

[1]Prof. ANUPAMA DIWAN

[1]Professor, School of Pharmaceutical Sciences,
Apeejay Stya University, Gurugram

[2]Manoj Kumar Sharma

[2]Assistant Professor, School of Pharmaceutical Sciences,
Apeejay Stya University, Gurugram

Ch. Id:-ASU/GRF/EB/NDDS/2022/Ch.01

DOI: https://doi.org/10.52458/9789391842871.2022.eb.grf.asu.ch.01

INTRODUCTION

It is well known that drug delivery systems (DDS) can benefit from the utilisation of polymers. The development of the majority of controlled-release technologies has been significantly aided by the ongoing and rapid advancement of research and development efforts pertaining to polymeric materials. An ever-increasing number of publications and patents in the field of controlled drug-release systems that make use of synthetic in addition to naturally occurring polymeric materials are evidence of the significant rise in interest that has taken place in this technology over the course of the previous quarter century. Various polymeric systems used in DDS as shown in Figure 1.1.

VARIOUS POLYMERIC SYSTEMS USED IN DDS

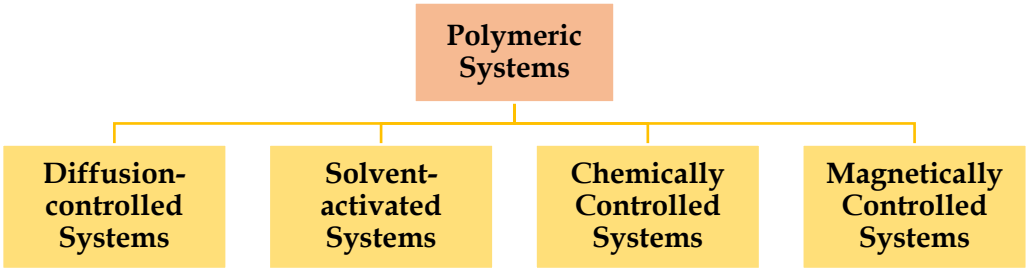

Figure 1.1: Polymeric Systems Used in DDS

Diffusion-Controlled Systems

There are two sorts of systems that are regulated by diffusion: the reservoir and the matrix. A drug core that is either powdered or liquid form is contained within a reservoir, which can have one of three common shapes: a sphere, a cylinder, or a disc. The core is surrounded by a layer of nonbiodegradable polymeric material, and it is through this material that the medicine progressively diffuses. The properties of both the drug and the polymer combine to determine how quickly the drug diffuses through the polymer and how quickly it is released into the bloodstream. The thickness of the polymer must be maintained at a constant level so that the delivery of the medicine can remain consistent. Due to the fact that the polymer is preserved after the medicine has been used up, the reservoir system presents a number of challenges, one of which is the requirement that the system be extracted from the body. It is possible for a significant quantity of the drug to be dumped into the bloodstream in the event that the reservoir

membrane is accidently ruptured, which is referred to as "drug dumping." This is yet another potential risk. The drug is dispersed evenly throughout the polymer matrix in a diffusion-control system that is of the matrix variety. This sort of system ensures that the drug is released from the matrix at an even pace as drug particles get detached from the polymer network. In contrast to the reservoir, such a system does not run the risk of medication waste being released into the environment in the event that the membrane is accidentally ruptured.

Solvent-Activated Systems

Osmotically controlled systems and swelling-controlled systems are the two categories that fall under the category of solvent-activated systems. An external fluid with a low concentration of a medication travels across a semipermeable membrane and into a zone inside the device where the drug is present in a high concentration as part of the osmotically regulated system. This takes place in a region. The concentration gradient that exists between one side of the membrane and the other is often reduced when osmotic pressure is applied. The passage of fluid in the opposite direction causes the dissolved drug to be expelled from the apparatus through a small orifice.

In the systems that are designed to limit swelling, the polymer is able to retain a significant amount of water without being dissolved. The structure of the system is that of a three-dimensional network formed from hydrophilic macromolecules that are cross-linked to one another. The permeability of such systems, for low molecular weight solutes, at a controlled rate as the polymer swells is one of the characteristics that distinguishes them from other types of systems.

Chemically Controlled Systems

The "pendant-chain" system and the bioerodible, or biodegradable, system are the two categories that are included in the category of chemically regulated systems. When the drug molecule is chemically connected to the backbone of the polymer, this type of system is referred to as a "pendant chain system." Within the body, in the presence of enzymes and other biological fluids, enzymatic cleavage or chemical hydrolysis takes place, and at the same time, the medicine is released at a rate that can be modulated. The medication may be attached to the polymer either directly or through the use of a "spacer group." In the bioerodible system, the controlled release of the medication is accomplished by the use of polymers that deteriorate over time. The medicine is disseminated evenly throughout the polymer, and when the polymer breaks down, it slowly releases the drug into the environment.

The polymers do not need to be removed from the body when the drug supply has been depleted, which is one of the most significant benefits of erodible systems; another benefit is that the medication does not necessarily need to be water-soluble. In point of fact, the use of biodegradable polymers in the future is projected to expand more than that of any other form of polymer in the future due to the aforementioned considerations.

Magnetically Controlled Systems

In cancer chemotherapy, one of the primary objectives has been to selectively target anticancer medicines while simultaneously limiting hazardous side effects. Systemic anticancer drugs that are used traditionally are unable to attain the level of tumour selectivity that is desirable. Albumin and magnetic microspheres are the two components that make up the magnetically responsive drug carrier systems that have been designed specifically for use in cancer treatment. Because of the magnetic properties that they possess, these microspheres have the potential to exhibit increased area-specific localisation in theory. This carrier system is versatile enough to accommodate a wide range of different medications. The magnetically responsive carrier system has a high efficiency for in vivo targeting in addition to a regulated release of a medication at the microvascular level. These are two of the primary advantages that the magnetically responsive carrier system has over other drug delivery methods. The use of polymers in the delivery of drugs has seen significant growth in recent years as a result of the tremendous breakthroughs that have been made in this area. We have segmented our research and development into the following areas in order to provide a better knowledge of the relationships and factors that affect specific polymers.

- Soluble polymers
- Biodegradable or bioerodible polymers
- Polymers that adhere to mucus membranes

SOLUBLE POLYMERS AS DRUG CARRIERS

Pinocytosis

Insoluble synthetic polymers are emerging as promising medication delivery carriers. Due to the increased number of potential target sites within the body, they appear to be more versatile than microparticle carriers. Biological membranes are efficient macromolecule barriers. The plasma membrane of the cell inhibits the loss of enzymes from the cytoplasm, while intracellular membranes demarcate subcellular

compartments with specific functions. Existing mechanisms for the translocation of macromolecules through membranes are often specialised and complex (e.g., pinocytosis).

Ideal qualities for a macromolecular drug carrier include:

- Sufficient drug loading capacity
- Retention of drug's water solubility after loading
- High enough molecular weight to allow glomerular filtration, but low enough to reach all cell types.
- Not caught by adsorptive pinocytosis is unaltered carrier.
- A durable carrier-drug connection in bodily fluids, but degradable in lysosomes
- A carrier that degrades slowly in the extracellular compartment or in lysosomes.
- Nontoxic
- Nonimmunogenic
- Biocompatibility

During pinocytosis, the cell membrane invaginates to form a membrane-bound vesicle that contains extracellular fluid, solutes, and sometimes substances adhering to the cell surface. After "pinching off" from the plasma membrane, the pinocytotic vesicle migrates into the cytoplasm, fusing with other incoming vesicles and ultimately fusing with lysosomes to form what is known as a secondary lysosome. Normally, all macromolecules entering the secondary lysosome are susceptible to the organelles' degradative activity. The monomeric constituents liberated during hydrolysis can usually pass through the lysosomal membrane for reutilization in anabolic metabolism or, alternatively, are lost from the cell. Large macromolecule-drug conjugates normally do not pass through cell membranes, but usually enter by pinocytosis. Drug conjugates that accumulate in lysosomes are termed "lysosomotropic." Coupling to a macromolecule automatically alters drug distribution. If the conjugate is passively captured solely as a solute, body distribution will depend on the rate of pinocytosis of individual cell types, as well as accessibility of the conjugate to each cell type. However, in those instances in which the conjugate has affinity for cell-surface receptors, and is therefore captured by adsorptive pinocytosis, the rate of uptake is dependent upon binding capacity. It is the latter carrier-mediated uptake that holds promise for targeting drug-carriers. To date, a number of cell-specific, receptor-mediated uptake processes have been identified. Many of these depend upon the interaction of specific carbohydrate moieties of a polymer with unique membrane receptors. If this type of approach, or other possible targeting systems (e.g., cell-specific antibodies),can be

incorporated as a homing device into the carrier vehicle, there is a real possibility of achieving selective targeting .Although pinocytosis of polymers is somewhat affected by the molecular weight of the polymer-conjugate, its rate of penetration into a cell may be increased to some extent by the incorporation of hydrophobic units, (e.g. binding tyramine or tyrosinamide to water-soluble polymers). Both approaches, however, lack specificity. The targeting of polymers requires either binding of specific antibodies or binding of saccharide units able to interact with receptors on the surface of certain cells. The binding of saccharide units on synthetic polymers is based on the fact that a small change in the structure of glycoproteins leads to changes in the fate of modified glycoproteins in the organism. It is possible to facilitate the transport of both natural and synthetic polymers into liver hepatocytes, Kupffer cells, fibroblasts, or macrophages.

Ideal Soluble Polymers:

The ideal drug carrier, as outlined by Duncan and Lloyd, would have controlled biodegradability in its polymer-drug linkages, an appropriate molecular weight range, the ability to incorporate residues that aid in targeting and efficient pinocytotic capture by target cells, no adverse toxic effects, and no persistence in the body. With the exception of biodegradability, synthetic polymers have advantages over their natural equivalents. Perhaps the most interesting characteristic of synthetic polymers is the huge choice that is accessible. There are several different kinds of copolymers outside homo-polymers, which are long chains of identical repeating units. Two or three distinct monomers may be copolymerized in a specific ratio. The resulting copolymer can have its monomers arranged in a variety of ways, such as random chains, or as repeating units of dimers or trimers. Pieces of two homopolymers are linked end to end to form a block copolymer. Cross-linking allows for the joining of several polymer chains; however, this typically results in the loss of water solubility.

Biodegradable Polymers:

In the 1960s, pioneering research in the field of regulated subdermal medication delivery began using biostable commercial polymers such as polyethylene and silicone rubber. The rate of drug release from the polymeric matrix or reservoir device was exclusively determined by diffusion. Biodegradation of the polymer was deemed an experimental variable that was less well-defined and unneeded. Consequently, biodegradable polymers gained popularity for two reasons. First, as the area transitioned from study to application, it became apparent that surgical removal of a drug-depleted delivery system was difficult, leaving nondegradable foreign components in the body for an extended amount of time, which posed an unwanted toxicological risk. Second, while diffusion-controlled release is an effective method for attaining predetermined drug

delivery rates, it is constrained by polymer permeability and drug properties. The creation of polymers with hydrolytically or enzymatically labile linkages has been a continuing endeavour, primarily in the pursuit of more absorbable sutures. Although absorbable sutures were first almost solely produced from various forms of collagen and evolved into current catgut, there has also been a growing emphasis on producing synthetic materials that hydrolyze to produce natural metabolites. Two materials have arisen as a result of these efforts: poly(lactic acid) and poly (glycolic acid).

Yolles and Sartori disclosed the first application of a synthetic biodegradable polymer for the systemic distribution of a medicinal substance in 1970. Since then, the focus has shifted to custom-synthesized biodegradable polymers, and a considerable body of literature on drug release from bioerodible polymers has been produced.

Three fundamental strategies have evolved:

- Erosion of the polymer surface accompanied by the simultaneous release of the physically entrapped drug
- Breakage of covalent bonds between the polymer and drug in the bulk or on the surface of the polymer, followed by drug diffusion; and
- Diffusion-controlled release of the physically entrapped drug, with delayed polymer absorption until after drug depletion. The third method eliminates the unreliability of the bioerosion rate and the difficulties of synchronising the diffusion and bioerosion processes to reach a predetermined delivery rate.

The following physicochemical characteristics contribute to the rate of polymer degradation:

1. Water permeability and water solubility, a reflection of the polymer's free volume and hydrophilicity, will determine the pace of hydrolysis and whether bulk or surface hydrolysis occurs. In the case of polyesters and ortho-esters, autocatalysis of the degradation process is feasible if acidic or basic groups are formed during polymer breakdown.
2. Crystallinity of the polymer; only the amorphous phase of the polymer is permeable (i.e., to water and drugs) and susceptible to enzymatic attack.
3. Glass transition temperature; the polymer's permeability and molecular chain mobility will reflect its glassy or rubbery character. Mobility of the chain appears to be a major determinant of vulnerability to enzymatic assault. Additionally, the inability of fragments to diffuse out of a glassy polymer will amplify an autocatalytic hydrolytic process. This may accelerate the breakdown of polymers such as polylactic acid and polyglycolic acid.

4. Physical parameters (e.g., size and surface-to-volume ratio); these appear to become important at the advanced stages of biodegradation, when phagocytosis may be involved.

Drug Release by Matrix Solubilization

Current enteric coatings, which can generally be classed as polyacids, fall within this group. They are water-insoluble before to ionisation of their carboxylic acid groups, but become more water-soluble after ionisation. Partially esterified copolymers of methyl vinyl ether and maleic anhydride or partially esterified copolymers of ethylene and maleic anhydride are among the most commonly researched systems. Esterified polymers undergo a regulated dissolution process in a constant pH environment and are therefore ideal materials for the controlled release of medicinal substances incorporated inside them.

Erodible Diffusional Systems

Erodible diffusional devices combine the characteristics of a rate-controlling polymer membrane, which offers a constant rate of drug release from a reservoir-type device, with erodibility, which causes bioerosion and eliminates the need for surgical removal of the drug-depleted device. Because consistent drug release necessitates that the bioerodible polymer membrane stay substantially unaltered during the delivery regimen, considerable bioerosion must not occur until after drug delivery is complete. The development of erodible diffusional systems has primarily focused on contraceptive steroid- or narcotic antagonist-releasing devices. Diverse aliphatic polysters, in particular polyethylene glycol, have been the most thoroughly studied polymer systems for subdermal capsules containing levonorgestrel (e-caprolactone).

Monolithic Systems

In monolithic systems, the medication is physically integrated into a polymer matrix and is released as the polymer bioerodes into the surrounding environment. In defining drug release from such systems, both polymer erosion and drug diffusion must be considered. If the drug's mobility in the matrix permits rapid diffusional release, its release kinetics will be first order. Zero-order release necessitates that the erosion process be restricted to the solid device's surface and that the drug be highly immobilised in the matrix. Although surface erosion is difficult to induce, these technologies offer a number of major benefits. Among these include the ability to modify drug delivery rate by only varying drug loading within the matrix, managing the device's lifetime, varying the device's physical dimensions, and the capacity of a single matrix to deliver a range of therapeutic agents.

Mucoadhesive Polymers

For many years, bioadhesive polymers have been utilised in both surgery and dentistry. These polymers include the well-documented "super glues," the esters of cyanoacrylates, which have applications ranging from osteochondral fracture repair to the capping of extraction wounds in dentistry. Other candidates for synthetic bone cement include polyurethanes, epoxy resins, acrylate, and polystyrene. Typically, the process of bonding for these bioadhesive polymers includes the establishment of covalent bonds with the target tissue to provide a permanent or semipermanent connection. In the creation of oral controlled-release dosage forms, the use of bioadhesive polymers that provide relatively short-term adhesion between the drug delivery system and the mucus or epithelial cell surface of the gastrointestinal tract may yield significant benefits. Therefore, binding will involve secondary forces, including hydrogen bonds and van der Waals forces. Mucoadhesives may therefore be considered a subset of bioadhesives. Polymer candidates must be nontoxic and nonabsorbable, immediately adhere to moist tissues, and release the integrated medication under control. Possibility exists that the capacity to localise a drug delivery system in a specific section of the GI tract could improve bioavailability, particularly for medicines with small absorption windows or instability in certain sectors of the tract. Both the extent and pace of drug absorption should be optimised by intimate contact with the target membrane. In general, alternative strategies for the regulation of GI transit of the dosage form, such as alteration of particle size and density as well as the use of fibrous components, have not proved effective.

Polymers Containing Pendant Bioactive Substituents

Bonding bioactive drugs to synthetic or naturally occurring macromolecules has been a significant strategy for enhancing their therapeutic efficacy while minimising their toxicity. Thus, many agents have been attached to numerous polymeric systems via degradable bonds. The original justification for this strategy was that systems may be designed to undergo hydrolysis or enzyme-catalyzed cleavages in the body in order to release the drug at a predetermined rate. As the rate of excretion of polymers with a large molecular weight is exceedingly sluggish, it was believed that agent/polymer adducts could serve as depots over lengthy periods of time. Earlier research in this field gave rise to the notion that polymeric systems could also be changed (e.g., by attaching a tumor-specific antibody) to exhibit great selectivity for target organisms such as cancers. In this instance, the modified polymer was intended to transport the active chemical to a particular location of action before releasing it. In essence, the systems were to work as guided missiles that seek out their targets. 87 With the exception of certain substituted

polyethyleneglycols, big macromolecules cannot readily enter the body through the gastrointestinal system or the skin. In actuality, a molecular weight between 5,000 and 10,000 is deemed sufficient to avoid significant absorption through skin or mucosal tissues. Therefore, adducts delivered orally or topically can only operate as depots. However, these systems can still provide significant benefits for targeted treatments of the gastrointestinal tract, eye, mouth, skin, vagina, etc. In these instances, a biostable polymeric carrier with a high molecular weight is desirable. Due to the moderate conditions seen in topically administered systems, the drug should be connected to the polymer via a bond that is highly sensitive to hydrolysis. For therapy of the GI tract, it is likely that an enteric coating would be required to prevent hydrolysis in the stomach from occurring prematurely. There have been numerous instances of successful agent targeting in vitro, but in vivo, there have been few successes. Goldberg et al.

Have enumerated the following antibody-targeting system problems:

- Antigen and antigen–antibody complexes in circulation
- Metabolic/biochemical alterations in adducts with activity loss
- kinetics of transport to tumour tissue versus competitive binding and metabolism
- Variable and heteroreactive antigenicity
- masking or interiorization of antigens unique to malignant cells

Various approaches to overcoming these problems include:

- Altering or eliminating
- Use of the immunoglobulin fragment (Fab') to avoid F-complement binding and minimise molecular size
- Therapy with intratumor and intravenous antibody adduct injections
- Surgical or radiation decrease of original lesion tumour burden in conjunction with systemic delivery of antibody adducts for eradication of metastases.

Direct injection and retention of soluble or insoluble systems into a specific region, such as a tumour, is a second method for targeting agent polymer adducts. Obviously, insoluble adducts will be retained by physical immobilisation. The usage of targeting moieties and the inclusion of pendant functional groups along the polymer backbone that can establish covalent connections with tissue carbonyl groups are two methods for maintaining soluble systems. There has also been usage of nonspecific electrostatic bonding between negatively charged cells and cationic adducts.

Matrix systems

There are a multitude of controlled-release devices that fall under this broad category. 104 Included are dissolved systems formed from a matrix containing a drug at or below the saturation solubility of the drug in the polymer, and dispersed systems containing the drug in a matrix at a concentration that considerably exceeds the saturation solubility of the drug in the polymer. In this example, the medication is believed to exist as distinct solid particles. This means that there are no macroscopic channels or pores in the polymer matrix after drug leaching. Other controlled-release technologies include porous matrix systems, which are created from a dispersion of drug particles and premade polymer. In porous matrix systems, it is thought that upon drug leaching, continuous macroporous pores or channels result from the displacement of the drug by the solvent.

The ease of fabrication is one of the key advantages of matrix devices over other forms of controlled-release drug delivery systems (such as reservoir devices). In general, matrix devices can be made by combining finely divided drug powder with prepolymer. This liquid is then poured into a suitable mould and allowed to harden. This method is particularly suitable for dispersed matrix devices, provided that the initial drug load is less than the drug's saturation solubility in the cured polymer. Due to the requirement to incorporate the barrier layer into the matrix, the production of reservoir-matrix devices is made more difficult. Typically, polydimethyl siloxane is utilised to fabricate dispersed-type matrix devices.

The advantages of this polymer for controlled-release systems include:

- It is an elastomer with good mechanical properties;
- It is highly permeable to hydrophobic solutes;
- It is nontoxic;
- It can be moulded into a wide variety of shapes and polymerized using straightforward techniques; and
- Its permeability is not affected by prolonged contact with biological fluids.

Its major disadvantages are

- It is impermeable to highly water-soluble solutes, particularly charged species;
- It elicits a modest foreign-tissue reaction following subdermal implantation; and
- The permeability of the polymer cannot be easily altered by modifying the polymer's composition.

- Due to the disadvantages of polydimethyl siloxane, a number of researchers have employed polymers derived from various hydroxyalkyl methacrylate derivatives.

These polymers provide numerous benefits, including:

- They are not harmful
- They elicit a minimal response to foreign tissue
- They are highly permeable to hydrophobic and water-soluble solutes, as well as charged species
- Their drug permeability varies depending on the copolymer composition and density of crosslinks

Additionally, hydroxyalkyl methacrylates and methyl methacrylate copolymers have been utilised. These copolymers have the advantage of increased mechanical strength and may offer some advantages in terms of their compatibility with blood and tissue. Other authors have employed numerous polymers, such as ethylene vinyl acetate, polyacrylamide, polyvinyl acetate, polyethylene, and polyether urethanes.

Heparin-Releasing Polymers

Gott et al. unintentionally initiated the groundbreaking work in heparin-controlled release materials. At the time, these researchers were evaluating a variety of materials for thromboresistance by venous implantation, and colloidal graphite produced the best results. Initially, these researchers believed that the thromboresistance was caused by the extreme smoothness of surfaces after graphite coating and the chemical inertness of colloidal graphite. These materials were sterilised by soaking them in a solution of benzalkonium sulphate. These graphite-benzalkonium-heparin (GBH) surfaces retained significant quantities of heparin even after three months of implantation in the venous system, according to additional research.

A significant disadvantage of GBH surfaces is that graphite can only be applied to rigid materials, as any flexing would compromise the integrity of the graphite coating and result in "peeling" of the GBH coating. To circumvent this issue, Leininger et al. chemically modified numerous polymer surfaces by forming permanent surface-associated quaternary ammonium groups, thereby eliminating the need for the adsorption of a cationic surfactant onto a hydrophobic surface, such as graphite, beforehand.

Depending on the type of polymer, three different surface treatments were used:

- Styrene chloromethylation, then quaternization with dimethyl aniline
- Radiation-induced grafting of vinyl pyridine to multiple polymers, followed by quaternization with methyl iodide or benzyl chloride.
- Incorporation of quaternizable monomers like vinyl pyridine into copolymer formulations

The surfaces were placed in a heparin solution after quaternization, and heparin was ionically bound to the ammonium groups. After exposure to fibrinogen, g-globulin, and albumin solutions, Zeta potential measurements revealed that the negatively charged surfaces became progressively less negative, which can be attributed to plasma protein adsorption. Rather than heparin release, the authors of these studies attributed the nonthrombogenic nature of the heparinized surfaces to changes in the plasma protein adsorption properties of the heparinized materials relative to the starting materials.

Merrill et al. ionically bound heparin to cellulose membranes via an ethyleneimine intermediate in order to produce heparinized cellulose membranes that could be utilised in kidney dialysis applications. The coupling of ethyleneimine to the hydroxyl groups on cellulose was accomplished through a number of distinct procedures. Pretreatment with ethylene oxide vapour to convert secondary cellulose hydroxyl groups into primary hydroxyl groups was followed by the reaction of ethyleneimine in toluene to produce aminated surfaces that could bind heparin ionically to the greatest extent. Plasma exposed to these substances exhibited lengthened clotting times. A disadvantage of ionically bound and physically dispersed heparin/polymer systems is that heparin is continuously depleted over time, thereby limiting the anticoagulant duration of such substances. Numerous researchers have covalently bonded heparin to polymer surfaces in order to produce long-lasting heparinized substances. For instance, a procedure has been described for radiation-grafting polystyrene to various polymeric materials. The surfaces of the resulting polystyrene are chloromethylated and then treated with an ammonia/alcohol solution to form benzylamine groups. The surfaces of polystyrene/benzyl-amine are then heparinized using a peratin/cyanuric chloride adduct.

Ionic Polymers

As drug carriers, ionic polymers include both soluble and insoluble (cross-linked) polymer systems. However, among the various ionic macromolecules, ion-

exchange resins have been studied the most. Although constant rate (zero-order) kinetics is not necessarily achievable with these systems, it is probable that future advancements in this field will employ ionic polymers as drug carriers for controlled delivery. Positively or negatively charged drugs combined with the appropriate ion-exchange resins produce insoluble polysalt resinates. Saunders and Srivastava recognised early on that the slow release of drugs from ion-exchange resins was a suitable strategy for the design of sustained-release preparations.

Oral administration is the primary route of administration for such resinate formulations. Orally administered ion exchangers are likely to be exposed to an acidic pH in the stomach for approximately two hours (1–2). They will then enter the intestine, where they will remain for at least six hours in a fluid with a slightly basic pH and an ion concentration equivalent to that of 0.1 N sodium chloride. The drug can then be slowly released through an exchange with ions such as sodium or chloride that are present in the GI fluid. Certain conditions must be met by drugs intended for prolonged-action dosage forms, particularly resinate formulations. Clearly, only drugs with acidic or basic groups in their chemical structure are eligible for consideration. The biological half-life (t 1/2) of to-be-formulated drugs should be between 2 and 6 hours.

There is likely no rationale for developing oral long-acting formulations of drugs with a half-life of eight hours or more. Active ingredients with a t 1/2 of 1 h or less are difficult to formulate into this dosage form if their usual single dose is high and their t 1/2 is less than 1 h. (e.g., more than 100 mg). It is necessary to determine whether the drug candidate is absorbed throughout the gastrointestinal tract. In the case of a limited absorption zone, the drug's bioavailability will be inadequate. The drug should also be sufficiently stable in gastric juice; if not, its therapeutic efficacy will be drastically diminished. For diagnostic purposes, both synthetic and natural polysaccharide-based ion-exchange resins have been utilised with success (e.g., gastric acidity). They have also been utilised as toxin adsorbents, antacids, and bile-acid binding agents. In addition to other therapeutic applications, they have been utilised effectively to treat liver diseases, renal insufficiency, urolithic disease, and occupational skin diseases. However, chronic use carries the risk of altering the ionic composition of the gastrointestinal fluids. Despite the numerous positive results reported in the scientific literature, the efficacy of drug resinates as sustained-release dosage forms has been called into question. For instance, researchers have analysed the use of resinate formulations critically.

Oligomers

Using oligomeric matrices instead of those with a high molecular weight to prepare drug derivatives can result in substances with significantly prolonged

pharmacological activity. In the case of oral administration, and possibly intradermal administration, the oligomeric matrix is frequently capable of transferring the active principles across physiological barriers, thereby facilitating absorption and enhancing bioavailability. Generally speaking, there are two ways to prepare oligomeric or polymeric derivatives of drugs: the preparation of a polymerizable derivative of the drug and the preparation of oligomeric or polymeric matrices with chemical functions capable of reacting selectively with a drug constituent. In general, the latter is more practical, since a single matrix can be used to prepare derivatives of multiple drugs. In addition, drug moieties frequently contain chemical functions that can interfere with polymerization processes. An intriguing variation on these techniques is to use the drugs themselves, resulting in polymeric or oligomeric products that are degradable in body fluids and revert to their parent monomers. Various oligomers and polymers have been reported as potential drug carriers.

Miscellaneous

The following polymers or polymeric materials have been investigated for their use in sustained-release medications:

1. Ethylcellulose and methyl stearate mixtures
2. Hydrated hydroxyalkyl cellulose
3. Salts of polymeric carboxylates
4. Chelated hydrogels
5. Water-insoluble hydrophilic copolymers
6. Cellulose ether compositions
7. Partial esters of acrylate-unsaturated anhydride copolymer
8. Water-soluble coating resins
9. Polymers with oxacycloalkane units
10. Polymers and copolymers of arylene-substitutes orthoesters
11. Polymers with alkoxy or oxacycloalkane substituents
12. Polyglycolic acid polyester condensates
13. Partial esters of polycarboxylic acids
14. Ionene-modified polymeric beads
15. Ethylene-vinyl acetate copolymers
16. Silicone polymer matrix having microsealed compartments
17. Gelatin nanoparticles

18. Serum albumin spherules
19. Phospholipid dispersionPolyglycolic acid sutures and films21. Polylactides
20. Dacron sutures
21. Caprolactone polymers and copolymers
22. Polysiloxane with N-vinylpyrrolidone
23. Hydrophilic acrylates or methacrylate polymers
24. Siloxane rubbers
25. Hydrocolloids
26. Amine-modified polyanhydrides
27. Polyelectrolytes or gelatin
28. Hydrophobic polycarboxylic acids
29. Metal cation cross-linked polyelectrolytes
30. Polymer–prostaglandin anticoagulant
31. Propranolol spheroids
32. Polymeric macrolides
33. Aspirin–polysiloxane-cellulose derivative matrix
34. Aspirin–pectin combinations
35. Iron compounds with natural resins
36. Polyacrylic alkali metal salts
37. Iron preparation with carboxylic polymers
38. Micronized insoluble cellulose
39. Furosemide–polystyrene
40. Glassy hydrophobic hydrogels
41. Beads containing acetaminophen
42. Acetaminophen using microcrystalline cellulose/wax formulations
43. Polyethylene glycol-derivatized superoxide dismutase
44. Poly(b-hydroxybutyrate), a copolymer with hydroxy valearate
45. Ibuprofen with acrylic polymers
46. Catecholamines using poly-(DL-Lactide-CO-glycolide)
47. Fenvalerate-poly-urea
48. Caffeine release using polyacrylate-methacrylate

49. Release of niclosamide and pituitary hormones using polymers
50. Theophylline and cimetidine using bioadhesive polymers
51. N-(2-hydroxypropyl) methacrylate copolymers
52. Alloys of hydrophilic-balanced copolymers
53. Collagen-poly hydroxyethylmethacrylate hydrogels
54. Ethylene vinyl acetate matrices
55. Hydroxyproline polyesters
56. Indomethacin in biodegradable polymers
57. Pluronic F-127, polaxamer
58. Pesticide chlordimeform in polymeric systems
59. Silicone–cellulose dispersions
60. Progesterone, testosterone, propranolol, and indomethacin from silicone matrices
61. Biodegradable fibers and tetracycline
62. Polymeric-pellet delivery systems for aquatic herbicides (e.g., fluridone65. Ethyl cellulose and ranitidine hydrochloride
63. Cyclodextrins for controlled release of insecticides, microbiocides,fungicides, pesticides, and polyorthoesters
64. Cellulose acetate trimellitate and phthalate
65. Hydropropyl methyl cellulose phthalate
66. N-(2-hydroxypropyl) methacrylamide
67. Ethylene-CO vinyl acetate
68. Glucoside monomers
69. Maleic anhydride/mono-methoxyoligoethylene glycol vinyl ether copolymers
70. Oligo(N-isopropylacrylamide)
71. N,N-dimethyl acrylamide

In veterinary products:

1. Enteric-coated swine vaccines
2. Rumen stable pellets (e.g., terpolymers of alkanolamine acrylates)polyamides of piperizine derivatives, and imidazoline-modified styrene acrylonitrile copolymers

Recent Advances

Using the Wurster process, aqueous polymeric dispersions for controlled drug delivery have been created. There have been reports of methods for producing sustained-release products from small-coated particles. Using Aquacoat® and Surelease® dispersions of propranolol as the model drug, the feasibility of obtaining aqueous polymer-coated bead formulations was investigated. By encapsulating a drug in a polymer, a delivery system utilising bioresorbable "Medisorb" polymers has been created. These microcapsules typically have a diameter of approximately 50 microns, which is small enough to be injected with a syringe. There are two possible microcapsule configurations. As the polymer of a monolithic delivery system degrades, the drug is continuously released in minute doses into the body. The second form delivers a concentrated dose of medicine to the body. Combining the two capsule forms into a single injection creates a comprehensive treatment profile that is especially beneficial for the administration of antibiotics. The rate of polymer dissolution is controlled by selecting lactide, glycolide, or a copolymer of the two. Different formulations of copolymer blends can yield drug-release times ranging from 7 days to 1 year. Synthesized biodegradable and bioabsorbable polymers can be used as a temporary scaffold for tissue regeneration, as a temporary barrier, or in controlled drug delivery systems. Polyester segments form the hard, crystalline blocks of the copolymers, while polyether glycol segments form the soft blocks of the segmented chains. Due to cost, stringent environmental regulations, and safety risks associated with the use of organic solvents in coating processes, the pharmaceutical industry has moved away from film-coating systems based on organic solvents. The industry is increasingly reliant on water-based coating formulations. Additionally, new aqueous polymeric dispersions have been developed, and intensive research is underway to maximise the use of water-dispersible colloidal particles in coating formulations. The development of controlled-release dosage forms whose mechanism of release is diffusion through a polymeric membrane formed by film coating necessitates the optimization of multiple processing and formulation variables to ensure reproducibility of the release rate. In the development and fabrication of transdermal drug delivery systems, numerous polymeric materials have been utilised. These materials have taken the form of device components and polymeric materials that are combined with drugs to slow or improve delivery. In reservoir-type transdermal devices, polymers have been utilised within the reservoir's contents and in the rate-limiting membranes to regulate the drug's passage across the skin. In matrix transdermal systems, polymers are used to create the device and to facilitate drug absorption through the skin. In adhesive-type systems, polymers have been used as adhesives and incorporated into the drug or device. Direct acylation

with succinic and glutaric anhydrides and the formation of a covalent bond with substituted aspartamide have been used to modify amantadine (PHEA). By hydrolyzing the conjugates, the quantity of amantadine in the copolymers was determined. PHEA-succinylamantadine appeared to bind to surfactant micelles more strongly than PHEA-glutarylamantadine. By absorbing Carbopol, a polymer carrier system has been developed to reduce the bitterness of erythromycin and its 6-O-methyl derivative, clarithromycin. The mechanism involves the ionic bonding of the amine macrolide to polyacrylic acid with a high molecular weight, which removes the drug from the solution phase in an ion-free suspension. The macrolide-Carbopol complexes were prepared by dissolving or slurring the drug and polymer in water or hydroalcoholic solutions at predetermined ratios. Human bioavailability studies have shown that microencapsulated Carbopol absorbates of erythromycin and clarithromycin provide blood levels comparable to those of conventional solid formulations.

CONCLUSION

As in the past, when certain ages were characterised by the discovery of major materials (such as the Stone Age or the Bronze Age), it has been suggested that the current era could be dubbed the Polymer or Plastic Age. The rapid expansion of scientific work and intense interest in the development of new drug delivery systems have provided strong motivation for the creation of polymers and new polymeric materials, particularly in the field of pharmaceutical applications. In contemporary research and drug delivery system design, the following entities have been intensively studied: soluble synthetic polymers, oligomers, copolymers, bioerodible and biodegradable polymers, polymer-coated liposomes, encapsulated drugs for cancer, colloid carrier systems, albumin and gelatin microspheres, magnetic microspheres and magnetically modulated systems, microsealed drug delivery systems, and matrix device systems.

Currently, osmotic pumps, implants, and dermal and oral drug delivery systems have seen the most significant advances in polymers and polymeric materials-based drug delivery devices. Exciting research in the field of polymers promises without a doubt the creation of new drug delivery systems. These systems will be designed for precise targeting and will be able to deliver precise and predictable systemic drug release with greater efficacy and fewer side effects. The multidisciplinary efforts of leading polymer researchers in the near future will undoubtedly result in the development of novel delivery systems in this rapidly expanding field.