chapter five

*Oral drug delivery**

Contents

* Adapted from Ranade, V.V., Drug delivery systems. 5A. Oral drug delivery, *J. Clin. Pharmacol.*, 31, 2, 1991 and 5B. Oral drug delivery, *J. Clin. Pharmacol.*, 31, 98, 1991. With permission of *J. Clin. Pharmacol.* and J.B. Lippincott Publishing Company, Philadelphia, PA.

I. Introduction

Historically, the most convenient and commonly employed route of drug delivery has been by oral ingestion. The original controlled release of pharmaceuticals was through coated pills, which dates back over 1000 years. Coating technology advanced in the mid- to late 1800s with the discovery of gelatin and sugar coatings. A major development in coating technology was the concept of coating drug-containing beads with combinations of fats and waxes. Since the mid-1900s, hundreds of publications and nearly 1000 patents have appeared on various oral-delivery approaches encompassing delayed, prolonged, sustained, and, most recently, controlled release of the active substance.[1]

The first truly effective oral drug delivery system, the "Spansule," was introduced in the 1950s. This prolonged-release system was marketed by Smith Kline & French Laboratories and consisted of small coated beads placed in a capsule. The 50 to 100 or more beads per capsule were designed to release at a different rate.[2]

In the mid- to late 1960s, the term "controlled drug delivery" came into being to describe new concepts of dosage-form design. These concepts usually involved controlling drug dissolution, but also had additional objectives. The primary objectives of a controlled-release system have been to enhance safety and extend duration of action. Today, we also have controlled-release systems designed to produce more reliable absorption and to improve bioavailability and efficiency of delivery.

An illustration of a controlled-release product designed to enhance solubility, absorption rate, and bioavailability is the antifungal drug griseofulvin. Dorsey has marketed a product called Gris-Peg, which is a molecular dispersion of griseofulvin in polyethylene glycol. This molecular dispersion has such enhanced-solubility properties that the dose of griseofulvin can be reduced by 50% over previously existing micronized powder forms of the drug. And, due to the higher blood levels produced, less frequent dosing of the drug is also possible.

An even newer concept of controlled release is that of site-specific release. New technology is also being developed that utilizes drug delivery systems capable of prolonged retention in the stomach or other body cavities, using bioadhesion and other factors to control not only rates of release, but also sites of release. In the 1970s, another concept of drug product design and administration has appeared: the therapeutic system. The objective of the therapeutic system is to optimize drug therapy by the design of a product that incorporates an advanced engineering systems-control approach.[3]

The modern controlled-release system is capable of producing not only sustained release, but also controlled release (i.e., a release rate that is not greatly influenced by the gastrointestinal environment). The oral controlled-release system is usually made of polymers, and the mechanisms of release are generally regulated by diffusion, bioerosion or degradation, and swelling or generation of osmotic pressure. Diffusion occurs when the drug–polymer mixture is exposed to the gastrointestinal fluid, resulting in release of the drug from the tablet or capsule. Bioerosion or degradation occurs with certain polymer–drug complexes when they pass through the gastrointestinal tract. Swelling or generation of osmotic pressure occurs with certain polymer–drug formulations when they are exposed to the gastrointestinal fluid, resulting in the release or expulsion of the drug.

The advantages of oral controlled-release products are as follows: decreased fluctuation of serum concentrations resulting in reduced toxicity and sustained efficacy; and decreased frequency of dosing resulting in improved patient compliance, reduced patient care time, and possibly reduced total amount of drug used. The disadvantages of oral controlled-release products are: longer time to achieve therapeutic blood concentrations, possible increased variation in bioavailability after oral administration, enhanced first-pass effect, dose dumping, sustained concentration in overdose cases (after oral administration), lack of dosage flexibility, and, usually, greater expense.[4]

When evaluating different proprietary controlled-release drug products, one will find that the absorption characteristics of each product are likely to be different from one another due to different mechanisms of release. Controlled-release preparations should generally not be considered bioequivalent or be substituted for one another, even though each product may contain a similar amount of an identical drug and meet the bioavailability requirements of the FDA. This consideration is especially important for drugs with narrow therapeutic ratios (e.g., antiarrhythmics, theophylline products, anti convulsants). However, if two drug products have similar bioavailability in addition to pharmacodynamics (i.e., therapeutic effect), substitution of such products should not cause any problem. Properties of drugs not suitable for controlled-release formulations are: very short or very long half-life, significant first-pass metabolism, poor absorption throughout the gastrointestinal tract, low solubility, and drug concentration not related to pharmacologic or therapeutic effect.

A controlled-release system is designed to produce a sustained concentration of a drug in the body. Many such products are now available, and following their introduction, oral drug delivery technology has enjoyed commercial success, with domestic sales approaching $1 billion. During the 1980s, more than two-thirds of the $20 billion U.S. drug market consisted of orally administered drugs, and more than 85% of that market was in the form of solid oral dosage forms. At present, a great opportunity lies in converting solid oral dosage formulations to controlled-release forms.[5]

Within the profitable and large solid oral drug market, major opportunities exist for marketing controlled-release formulations of several categories of drugs. Drugs that are taken on a chronic or extended basis — cardiovascular, arthritic, respiratory, and analgesic products — often have the most potential for controlled-release delivery improvements. The oral controlled-release drug delivery market is currently small, but growing rapidly, with total sales of more than $500 million. This market segment is fueled by an emerging trend in the drug industry favoring controlled-release products and improved drug delivery systems.

In order to gain a better understanding of the factors involved in developing controlled-release oral drugs, it is worthwhile to understand some of the basic elements of gastrointestinal (GI) physiology, particularly as they pertain to the mechanisms and factors influencing drug absorption and GI transit time.

These factors have had a profound influence on the design of oral controlled drug delivery. As our understanding of GI physiology increases, it should be possible to develop strategies for controlled drug delivery on the molecular or cellular events that are critical in overcoming the limitations of this technology.[6]

II. Features of the GI tract

While a number of drugs are in sustained-release form and have an intended site of action in a local region of the GI tract, the overwhelming majority of oral drugs are targeted to act elsewhere in the body. Thus, the GI tract is usually a conduit to get the drug to the bloodstream. For oral dosage forms, it can, therefore, be assumed that the focus is primarily on the temporal aspects of drug release.

It is assumed that a constant level of drug in the blood for a specified period of time is a desired end point. This is most easily accomplished by direct administration of a drug by IV drip, where the rate of drug administered is adjusted, based on the pharmacokinetic properties of the drug, to achieve an invariant, steady-state level. In the simplest concept, the rate of drug administration is computed on the basis of replacement. Thus, the rate of drug elimination is the same as the rate of drug administration, which, in turn, is the product of the desired blood level of the drug. An assumption is usually made that drug levels in the bloodstream parallel the apparent

volume of distribution of the drug and the first-order elimination-rate constant for the drug.[7]

For routes involving drug absorption, such as the oral route, an absorption phase is introduced prior to appearance in the blood. However, this does not change the approach used in computing the desired rate of release of drug from the dosage form to achieve a constant level in the blood. Thus, the rate constant of drug release from an oral sustained-release dosage form will be computed in exactly the same manner as previously mentioned. However, since a lag time has been introduced in getting the drug to the blood (i.e., the absorption phase) it is necessary to make some adjustments in computing the total amount of the drug that will be contained in the dosage form. It is therefore common to see a sustained-release oral system composed of two parts: an immediately available dose used to establish therapeutic levels of the drug quickly, and a reserve portion that is intended to slowly release the drug for eventual absorption and maintenance of constant blood levels. The total drug, therefore, is the sum of immediate and reserve forms. It is also clear that a zero-order rate of drug release will commonly be used to sustain levels of the drug. Thus, the total amount of reserve drug will be equal to the zero-order release-rate constant multiplied by the total number of hours of sustained effect desired.[8]

It should be pointed out that there are a number of constraints on the design of oral controlled drug delivery systems: dose size, drug molecular size, charge and pKa, aqueous solubility, partition coefficient, stability, absorption, metabolism, half-life, margin of safety, toxicity, and clinical response.[9]

III. Targeting of drugs in the GI tract

The GI tract is the preferred site of absorption for most therapeutic agents as seen from the standpoints of convenience of administration, patient compliance, and cost. The majority of oral dosage forms consist of tablets and capsules, which are often provided as instant-release systems designed to disintegrate rapidly in the stomach.[10] The dissolved drug substance is usually absorbed from the small intestine. The efficiency of these processes of release and uptake is dependent upon the physicochemical characteristics of the drug (e.g., solubility, stability in acid and alkaline environments, permeability through GI membranes) as well as physiological variables, such as GI transit time.[11]

Briefly, the approach has been to consider the distance a dispersed drug has to pass down the small intestine before the total available dose is absorbed. Mathematical analysis has shown that the more efficient the dissolution and absorption processes, the greater the reserve length. Whether the small intestine alone should be taken as the predominant absorption site is debatable. The opinions presented in the literature suggest that absorption of drugs from the large bowel is often poor and erratic. However, recent

studies conducted on beta blockers indicate that the large intestine may have a more significant contribution to total absorption than hitherto realized.[12]

Controlled-release dosage forms are gaining rapid popularity in clinical medicine. The more sophisticated systems are used to alter the pharmacokinetic behavior of drugs in order to provide twice- or once-a-day dosage. Other applications include enteric coatings for the protection of drugs from degradation within the GI tract or the protection of the stomach from the irritating effects of the drug, and the delivery of drugs to so-called absorption windows or specific targets within the GI tract, particularly the colon.

Much about the performance of a system can be learned from *in vitro*-release studies using conventional and modified dissolution methods. However, an essential stage in development must also be a subsequent evaluation *in vivo*. Davis has used the noninvasive technique of gamma-scintigraphy to follow the GI transit and release characteristics of a variety of pharmaceutical dosage forms in human subjects. Such studies not only provide insight into the fate of a dosage form and its integrity, but also allow a correlation to be made between the position of a system in the GI tract and resultant pharmacokinetic profiles. Davis has also studied methods for the evaluation of the fate and performance of orally administered dosage forms:[10] radiology (x-ray), endoscopy, radiotelemetry, epigastric impedence, gamma-scintigraphy, and deconvolution of pharmacokinetic data.

GI motility presents a major impediment to the development of devices necessary for site-specific drug release. This is most easily overcome in the large intestine, where conditions are most predictable and quiescent. Targeting delivery to the stomach is technically more difficult due to the power of gastric movement during both the digestive and interdigestive phases. Buoyancy, dimensional change, mucosal adhesives, and drugs such as propantheline and fatty excipients have all been suggested as methods of ensuring gastric retention of small formulations. The carcinogenic nature of nitrosamines derived from the interaction of nitrates in food with secondary or tertiary amines in both food and drugs has prompted the delivery of N-nitroso-blocking agents to the stomach.[13]

The "hydrodynamically balanced system," for example, derives its effect from hydration and swelling, which entrap significant quantities of air and confer a density that is less than that of gastric fluid. This buoyancy is claimed to greatly extend residence time in the stomach, thereby allowing the N-nitroso blockers to diffuse. More specific targets for delivery within the small intestine include the duodenum, for the preferential absorption of peptides and proteins, by exploiting known facilitated transport mechanisms for dipeptides and tripeptides, as well as the delivery of antigens and allergens to M-cells residing in the Peyer's Patch regions.[14]

There is growing interest in the specific delivery of drugs to the colon, either for local treatment, such as that of ulcerative colitis and irritable bowel syndrome, or for the systemic delivery of compounds that are normally not well absorbed from the GI tract by exploitation of the long residence time in the colon.[15] It is possible to modify the absorption characteristics of the

colon using a variety of absorption enhancers, including mixed micelles. Clearly for such applications, sophisticated delivery systems will need to be developed that will allow site-specific delivery of not only the drug, but also the absorption enhancer.

IV. Mathematical models for controlled-release kinetics

The controlled release of drugs can be achieved by incorporating solutes, either in dissolved or in dispersed form, in polymers. During the design stage of these formulations, it is desirable to develop and use simple yet sophisticated mathematical models to describe release kinetics. From a mathematical modeling point of view, controlled-release systems can be classified according to the physical mechanisms of the release of the incorporated solute. Mathematical modeling of the release kinetics of specific classes of controlled-release systems may be used to predict solute release rates from and solute diffusion behavior through polymers and to elucidate the physical mechanisms of solute transport by simply comparing the release data to mathematical models.

Peppas[16] has discussed diffusion-controlled, osmotically controlled, and chemically controlled systems. Diffusion-controlled systems contain a reservoir, matrix, and porous membrane. In chemically controlled systems, shrinking core models provide the most accurate description. Hopfenberg[17] has derived expressions for solute release from erodible slabs, cylinders, and spheres. Mathematical models exist for erodible systems in which solute release from the surface is also important. These have recently been discussed by Lee.[18]

V. Design and fabrication of oral delivery systems

The overwhelming majority of controlled-release systems rely on dissolution, diffusion, or a combination of dissolution and diffusion to generate slow release of a drug. Starting with limited data on a drug candidate for a sustained-release system, such as dose, rate constants for absorption and elimination, and some elements of metabolism, one can compute a desired release-rate for the dosage form, and the amount of drug required.[19–21]

While the desirability of having a correlation between *in vivo* bioavailability and *in vitro* release is obvious, many, if not most, sustained-release products do not show such a correlation unless one varies *in vitro* experimental conditions. Thus, when a correlation is found for a particular drug in a particular dosage form, it cannot be applied to another drug or dosage form. The correlation becomes better when the *in vitro* test is done in a pH gradient rather than distilled water. Furthermore, optimization of test conditions can also help minimize variations. A number of such systems have been described and utilized.[22–24]

Within the scope of this review, a variety of controlled-release systems are discussed. Included among these are the following:

1. Dissolution-controlled release
2. Osmotically controlled release
3. Diffusion-controlled release
4. Chemically controlled release
5. Miscellaneous controlled release

A. Dissolution-controlled release

The most important attribute of membrane-controlled drug delivery systems is their ability to maintain a constant rate of drug delivery over a reasonably long period of time. The duration of constant drug delivery must be compatible with physiologic constraints and the route of administration. For example, while a duration of several weeks may be appropriate for a membrane-controlled implant, it is much too long a time frame to consider for an oral dosage form. Clearly, the selection of a membrane system or its duration of action must be based on an appropriate set of conditions. It may well be that a constant input rate of a drug provides little real advantage over well-controlled, first-order mechanisms under certain biopharmaceutic conditions. On the other hand, there are certainly situations that call for membrane-controlled systems that provide constant rate input for time frames ranging from several hours to several months.[25]

The oral route of drug administration presents its own unique set of problems and constraints. The time frame, or "window," for absorption is limited to the total GI residence time. Even this time may be an overestimate if the drug in question is absorbed only in certain segments of the GI tract. Moreover, individual differences in residence time and motility patterns are generally quite large. Taking into account gastric emptying and small and large intestine transit time, it would seem that a reasonable duration in the GI tract is approximately 24 hours. The absorption, distribution, and elimination of drugs are normally simplified by considering them all to be simple first-order processes. Given the average 24-hour residence time and high individual variability in the GI tract, only drugs with relatively short elimination half-lives should be considered for membrane-controlled reservoir systems.

In sustained-release formulations employing dissolution as the rate-limiting step, drug release is controlled by dissolution of a polymer or by a chemical reaction with a soluble subunit. Individual particles or granules containing a drug can be uniformly dispersed in the matrix or coated with varying thicknesses of coating material resulting in dissolution and release of the drug over extended periods of time. If the dissolution process is assumed to be diffusion-layer controlled, in which the rate of diffusion from the solid surface to the bulk solution is rate-limiting, the flux is the product of the diffusion coefficient and the concentration gradient from the solid surface to the bulk solution side. Flux can also be defined as the flow rate of material through a unit area.

With encapsulated dissolution control, the drug may be coated with slowly dissolving polymeric materials. Once the polymeric membrane has

dissolved, all the drug inside the membrane is immediately available for dissolution and absorption. Thus, drug release can be controlled by adjusting the thickness and the dissolution rate of the polymeric membrane. If only a few different thicknesses of the membrane are used, usually three or four, the drug will be released at different, predetermined times ("pulses"). If a spectrum of different thicknesses is employed, a more uniformed sustained release can be obtained.[26]

Membrane-coated particles can be directly compressed into tablets or placed in capsules. If the particles are compressed into a tablet, fracture of some of the surfaces generally occurs, with a resultant increase in release rate. It is a common practice to employ 1/4 or 1/3 of the particles in nonsustained form (i.e., particles without a barrier membrane) to provide for immediate release of the drug. Alternatively, a portion of the drug can be placed in a rapidly dissolving coating membrane to quickly establish therapeutic levels. One of the principal methods of coating a drug is microencapsulation, wherein the drug solution or crystal is encapsulated with a coating substance. The most common approach for microencapsulation is coacervation, which involves the addition of a hydrophilic substance to a solution of colloid. Whether a drug is water-sensitive or not, it can be microencapsulated if the drug is protected from the aqueous environment by coating with polymers, such as ethylcellulose, cellulose acetate phthalate, or carnauba wax prior to microencapsulation.

The thickness of the coat can be adjusted from 1 to 200 μm by changing the amount of coating material from 3 to 30%. Microencapsulation has the additional advantage that sustained drug release can be achieved with taste abatement and better GI tolerability of microencapsulations. Good examples are microencapsulated aspirin and potassium chloride. In both cases, drug effects from the microencapsulated dosage forms are more prolonged and less irritating than the same amount taken as ordinary tablets. Both formulations show the same total drug absorbed, as calculated from the area under the curve. One of the disadvantages in employing microencapsulation is that no single process can be applied to all core-material candidates. Moreover, incomplete or discontinuous coatings can cause unstable and irregular release characteristics.[27]

Sears[28] applied synthetic phospholipids as a coating material to obtain sustained release from microcapsules. The synthetic phospholipids, when the polar moiety of the phosphatidylcholine head group was altered, showed a decreased rate of hydrolysis by phosphorylase C. These compounds have been employed as surfactants and encapsulation agents for drugs such as insulin, which require protection from hydrolysis in the stomach. Microorganisms have also been used as microcapsules. Yeast, molds, or other fungi that synthesize fat within themselves can absorb fat-soluble drugs and prolong their potency.[29]

With matrix dissolution control, the two general methods of preparing drug–polymer particles are congealing and aqueous-dispersion methods. In the congealing method, the drug is mixed with polymeric substances or

waxes. The wax- or polymer–drug material can be cooled and put through a sieve to obtain the correct particle size, or it can be spray-congealed. Kawashima et al.[30] used a modified spherical agglomeration technique as an alternative to the spray-congealing method. In the aqueous-dispersion method, the drug–polymer mixture is sprayed or placed in water and then collected. Usually, the aqueous-dispersion method shows a higher release rate than wax congealing or spraying, probably due to the increased area and entrapment of water.

Recently, Heller and Trescony[31] synthesized a methyl vinyl ether-maleic anhydride copolymer that has extraordinary sensitivity to the surrounding pH. These polymer systems have a characteristic pH, above which they are completely soluble and below which they are completely insoluble. The specific pH depends on the size of the alkyl group in the copolymer ester. The polymer dissolution and drug release can be strictly controlled to fit any desired pH environment. These systems have the potential, therefore, to be used in oral controlled drug delivery cases in which absorption at a specific site in the GI tract is desired.

Zero-order release at a particular site in the GI tract can be achieved by maintaining the pH of the system. Theeuwes and Higuchi[32] prepared sustained-release procainamide in matrix forms and compared the release rate to that of IV dosing. The rate of absorption *in vivo* correlated well with *in vitro* dissolution. A variety of slowly dissolving coatings, based upon various combinations of carbohydrate sugars and cellulose, polymeric materials and wax, are also available.

B. Osmotically controlled release

In addition to the mechanism of solution diffusion, drug release from a membrane-reservoir device can also take place through a membrane via an osmotic pumping mechanism. In this case, a semipermeable membrane, such as cellulose acetate, is utilized to regulate osmotic permeation of water. With constant reservoir volume, this type of device delivers a volume of drug solution equal to the volume of osmotic water uptake within any given time interval. The rate of osmotic water influx, and therefore the rate of drug delivery by the system, will be constant as long as a constant thermodynamic activity gradient is maintained across the membrane. However, the rate declines parabolically once the reservoir concentration falls below saturation. Such an osmotic delivery system is capable of providing not only a prolonged zero-order release, but also a delivery rate much higher than that achievable by the solution-diffusion mechanism. Osmotically controlled release is also applicable to drugs with a wide range of molecular weight and chemical composition, which are normally difficult to deliver by the solution-diffusion mechanism.

There are basically two types of osmotic delivery devices, namely, the miniosmotic pump and the elementary osmotic pump. In the miniosmotic pump delivery system, the drug reservoir is separated from the osmotic

agent compartment by a movable partition. At the other end of the osmotic compartment is a semipermeable membrane, and a rigid impermeable material forms the remaining three sides of the pump, with a delivery orifice at the front. In contrast, the elementary osmotic pump consists of an osmotic core containing the drug, surrounded by a semipermeable membrane with a delivery orifice. The delivery rate from these devices is regulated by the osmotic pressure of both the osmotic agent of the core formulation and by the water permeability of the semipermeable membrane.[33]

Unlike the solution-diffusion mechanism, the osmotic delivery system involves a volume flux of water across a semipermeable membrane. In the miniosmotic pump system, as long as a large enough reservoir is present, the delivery of dissolved drug at any concentration can be zero-order because of the separate compartmental design. In the elementary osmotic pump, since the core formulation is also the osmotic driving agent, the delivery rate is constant as long as excess solid is present within the drug reservoir.

Osmotically controlled drug release requires only osmotic pressure to be effective, and is essentially independent of the environment. As a consequence, this should be an excellent sustained-release system for oral dosage forms. Thus, the drug delivery rate for an oral osmotic therapeutic system can be precisely predetermined regardless of pH change. In fact, the delivery rate of sodium phenobarbital from this system into artificial gastric juice at pH 2 and intestinal fluid at pH 7.5 (containing no enzymes) was shown to be pH-independent.[34]

The development of an OROS system refers to the quality of a therapeutic system designed to control pharmacologic effects through control of plasma concentrations. This can be judged through the constancy of drug concentrations during its use. The flatness of plasma-concentration curves can be expressed by the ratio of maximum to minimum concentration within one dosing interval at a steady state for repetitive injections. For plasma concentrations obtained following the administration of a therapeutic system, this ratio is, in addition to pharmacokinetic constants and dosing interval, a function of the system's design parameters and is called the dosage form index, or DI.[35]

During selection of a drug substance for delivery via the OROS system (developed by Alza Corporation), one also needs to consider the site of entry and factors that can modify the rate and extent of drug absorption en route from that site to the target tissue. Considering that the OROS system is a solid, tablet-sized object, it will pass through the GI tract within the transit time of foodstuff. To reduce drug plasma-concentration fluctuations on repetitive administration of an OROS system, it is also necessary to consider the half-life associated with the distribution phase. Some drugs, such as lithium, are rapidly absorbed but are distributed slowly in the tissues, giving rise to sharp absorption peaks following administration. For lithium and many other drugs, such peaks are associated with side effects that can be prevented by administration in a controlled-delivery dosage form (see Figure 5.1).

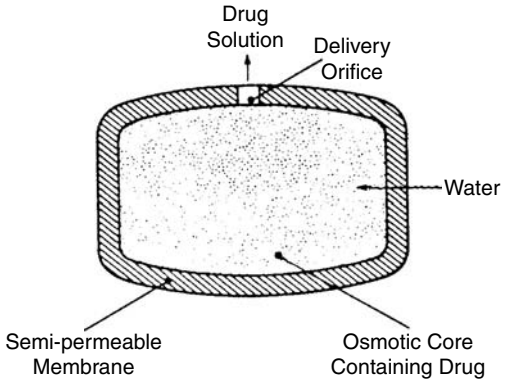

Figure 5.1 Cross-sectional diagram of an OROS system. (Reprinted with permission from *Annual Reports in Medicinal Chemistry,* Vol. 15, Academic Press, New York, 1980, 308 and Alza Corporation, Palo Alto, CA.)

Theophylline is a drug that has the desired attributes for delivery via the OROS system. It is used primarily for the treatment of obstructive airway disease (e.g., asthma). Its pharmacokinetics and pharmacodynamics in man have been well documented. In particular, its pharmacology has been studied over a wide range of plasma concentrations during intravenous administration of aminophylline (a form of theophylline).[36] These and other studies have shown that the OROS system allows safe and effective delivery of theophylline and creates less need for individual dose adjustment than a system with a higher DI.

A currently marketed over-the-counter (OTC) appetite suppressant, Acutrim®, incorporates Alza's OROS system. In Acutrim, the active ingredient (phenylpropanolamine) is released at a controlled rate. Another benefit of controlled rate delivery of Acutrim is that, in this form, phenylpropanolamine does not produce the adrenergic-like side effects that are normally seen in other conventional formulations.

For insoluble or extremely soluble drugs, Alza Corporation has designed another system, the "push-pull" OROS. This system has two compartments, one containing an osmotic agent and the other containing the drug. A semipermeable membrane surrounds both. In the GI tract, water enters each compartment through the membrane at a different rate. In the drug compartment, soluble drugs are formulated into solutions and insoluble ones into suspensions. As water enters the other compartment, it expands and pushes against the drug compartment. This causes the drug solution or suspension to be released at a controlled rate through the orifice in the membrane surrounding the drug compartment.

Elan Corporation of Ireland has developed its own osmotic pressure system called MODAS. MODAS stands for Multi-Directional Oral Absorption System. MODAS is similar to OROS in some respects, yet quite different

from it in others. Like OROS, this system consists of a tablet core surrounded by a semipermeable membrane. However, unlike OROS, MODAS has a multitude of small pores through which the drug solution can exit. The rate of drug-solution release can be controlled by the composition of the membrane. Since the drug release is multidirectional, concentration of the drug in any one area of the GI tract is avoided. Elan has identified a number of drugs that are suitable for MODAS, including alphamethyldopa, ibuprofen, theophylline, quinidine, indomethacin, potassium chloride, and naproxen.

C. *Diffusion-controlled release*

The most commonly used type of membrane material in drug delivery systems is homogeneous films of amorphous and semicrystalline polymers above their glass transition temperatures. Drug transport occurs by dissolution in the membrane at one interface, followed by diffusion down a concentration gradient across the membrane and, finally, release from the second interface into the external medium. Such a solution-diffusion membrane is typically observed in hydrophobic membrane materials, such as silicone rubber and ethylene vinyl acetate copolymer. A similar mechanism is also responsible for drug permeation through most swollen hydrogel membranes.[16]

The rate of drug permeation through solution-diffusion membranes is directly proportional to the product of the drug-diffusion coefficient in the polymer and the polymer/solution partition coefficient. The former is a kinetic or nonequilibrium transport parameter, while the latter is an equilibrium thermodynamic property. Despite progress in estimating diffusion and partition coefficients of simple gases in polymers, no reliable method is presently available for the quantitative prediction of both the diffusion and partition coefficients of more complicated organic molecules in polymers. Nevertheless, various trends can be identified based on accumulated experimental evidence in the literature.

Above the polymer glass transition temperature, drug diffusion coefficients in a polymeric medium generally decrease with increasing drug molecular weight, molecular size, crystallinity of the polymer, and the amount of filler in the polymer. On the other hand, the drug-diffusion coefficient will increase with more plasticizer content and solvent swelling in the polymer. Other parameters, such as copolymerization, cross-linking, and grafting, as well as the distribution and orientation of crystallites, may either increase or decrease the observed drug-diffusion coefficient. In some instances, the concentration dependence of the diffusion coefficient may further complicate the situation.[37]

With regard to solubility and partitioning effects, one generally observes that a drug will be more soluble in the polymer phase as the difference in the solubility parameters of the drug polymer becomes smaller. Michaels et al.[38] have demonstrated that steroid permeability in polymers can be correlated with thermodynamic parameters, such as the melting temperature of the steroid and the solubility parameters of the steroid and polymer. The

Table 5.1 Different types of commercially available osmotic systems

(I) Osmotic pumps for experimental research	
ALZET (Durect Corp., USA)	Miniature, implantable osmotic pumps for laboratory animals. Commonly implanted subcutaneously or intraperitoneally, but, with the help of a catheter, can be used for intracerebral, intraveneous, and intraarterial infusion. Different models having delivery rates from 0.25 to 10 μ1/h and durations from 1 day to 4 weeks available. Delivery profile independent of drug formulation.
OSMET (Durect Corp.)	Used as experimental tools for human pharmacological studies and can be used for oral, rectal, or vaginal administration. Delivery profile independent of drug formulation, and it is available with release rates ranging from 8 to 20 μ1/h.
(II) Osmotic pumps for humans	
Oral	
Elementary osmotic pump (Alza Corp., USA)	Single-layer tablet for delivery of drugs having moderate water solubility. Can be utilized for zero-order delivery as well as pulsed release.
Push–pull osmotic pump (Alza Corp.)	Bilayer tablet used to deliver drugs having low to high water solubility. Products such as Ditropan XL (oxybutynin chloride), Procardia XL (nifedipine), and Glucotrol XL (glipizide) are based on this technology. Number of modifications available, such as delayed push–pull system, multilayer push–pull system, and push–stick system.
L-OROS (Alza Corp.)	Designed to deliver lipophilic liquid formulations and is suitable for delivery of insoluble drugs.
OROS-CT (Alza Corp.)	For targeted delivery to colon; can be used for local or systemic therapy.
Portab System (Andrx Pharmaceuticals, USA)	Tablet core consists of soluble agent, which expands and creates microporous channels for drug release.
SCOT (single composition osmotic tablet, Andrx Pharmaceuticals)	Utilized various osmotic modulating agents and polymer coatings to provide zero-order release.
ENSOTROL drug delivery system (Shire Labs, Inc., USA)	Utilized various solubilizing and wicking agents for delivery of poorly water-soluble drugs.
Zero-Os tablet technology (ADD Drug Delivery Technologies AG, Switzerland)	Specifically for delivery of lipophilic compounds. Consists of gel-forming agents in the core that forms gel after coming in contact with water, and drug is released as a fine dispersion.

Table 5.1 Different types of commercially available osmotic systems (Continued)

Implantable	
DUROS (Durect Corp.)	Miniature (4 × 45 mm), implantable osmotic pumps for long-term, parenteral, zero-order delivery of potent therapeutic agents. Delivers drugs at a precisely controlled and constant rate within therapeutic range for long periods. Viadur (leuprolide acetate), a successful product in the market, delivers leuprolide continuously at a nominal rate of 125 μg/day over 1 year for palliative treatment of prostate cancer. DUROS sufentanil (3 months continuous delivery for treatment of chronic pain) and DUROS hydromorphone (for continuous delivery to the spine) are in various developmental phases.
(III) Osmotic pumps for veterinary use	
VITS (veterinary implantable therapeutic system, Alza Corp.)	Designed to deliver drugs at a controlled rate in animals for a period of 1 day to 1 year, and can be implanted subcutaneously or intraperitoneally in any ruminant, nonruminant, companion, or production animals. Available in various sizes (2–10 mm in diameter) and can be designed to give delivery rates from μg/day to mg/day. Drug is kept isolated from body fluids and thus can be used to deliver water-labile compounds (e.g., proteins and peptides).
RUTS (ruminal therapeutic system, Alza Corp.)	For controlled delivery of drugs up to one year in the rumen of cattle and sheep. Up to 10 g of drug can be administered. Generally, 2–3 cm in diameter and up to 10 cm in length, but larger dimensions are possible, depending upon application. Can be designed for zero-order delivery of up to g/day. Ivomec SR (ivermectin) and Dura SE (sodium selenite) available commercially.

Source: With permission, Elsevier, *J. Control Rel.*, 79, 7–27, 2002.

partition coefficient, defined as the ratio of the drug concentration in the external solvent medium, may also be concentration-dependent.

Many of the partition coefficients reported in the literature have been measured in saturated drug solutions and subsequently used in situations where the drug concentration may deviate from saturation considerably. Depending on the nonlinearity involved in the absorption isotherm, such practice can lead to appreciable error in the determination of permeation parameters. Therefore, for the design of a specific membrane-reservoir drug delivery system, it is necessary to determine both the drug diffusion and partition coefficients experimentally. Preferably, one should also carry out selected experiments over the entire concentration range of interest so that any concentration dependence can also be established.

Being cross-linked and hydrophilic, hydrogel polymers are unique in that they are quite glassy in the dry state, whereas in the presence of water they can swell significantly to form an elastic gel. In addition to having good biocompatibility, their ability to release drug in aqueous media and the ease of regulating such drug release by controlling the water swelling and cross-link density make hydrogels particularly suitable as carrier matrices or rate-controlling membranes in the controlled release of pharmaceuticals.

A typical hydrogel membrane device usually consists of either a solid core of drug or a slightly cross-linked hydrogel matrix containing dissolved or dispersed drug, and a surrounding rate-controlling hydrogel membrane. In both cases, the membrane can be either prefabricated or coated and subsequently polymerized. When a hydrogel matrix is used as a drug reservoir, a rate-controlling membrane can also be formed by a newly developed interpenetrating network (IPN) technique. In this case, the surface layer of the matrix is first treated with heat or UV irradiation or via *in situ* olycondensation generated by immersion in a second reactant solution producing a less permeable, rate-controlling membrane layer.[39–41]

For other, specific purposes, hydrogel-membrane devices may be stored in either dry or hydrated states. The release of water-soluble drugs from initially dry hydrogel membrane devices generally involves the swelling of the membrane and subsequent dissolution or swelling of the core. In the case of a membrane originally saturated with a drug, a simultaneous absorption of water and release of a drug via a swelling-controlled diffusion mechanism is also observed. Thus, as water penetrates a glassy hydrogel membrane device, the polymer swells and its glass transition temperature is lowered. At the same time, the dissolved drug diffuses through this swollen flexible region into the external releasing medium.[42,43]

Yasuda et al.[44] have derived a theoretical expression relating the solute diffusion coefficient in a water-soluble polymeric membrane to the free volume and degree of hydration in the membrane. Conformity of experimental results to the theory suggests that the permeation of solute occurs predominately through the porous regions of the network. As pointed out by Yasuda et al., these porous, water-filled regions through which the transport of permeant can occur may only be conceived as fluctuating pores or channels of the polymer matrix, which are not fixed either in size or location.

Zentner et al.[45] have studied the effect of a cross-linking agent on progesterone permeation through swollen hydrogel membranes. In addition to the decrease in progesterone-diffusion coefficient with increasing cross-linker, they found that at low concentrations of the cross-linker, the chain length of the cross-linker did not affect the "fluctuating-pore" permeation mechanism. However, at high concentrations of cross-linker, the diffusion coefficient of progesterone in the system with a shorter cross-linker, ethylene glycol dimethacrylate, was relatively independent of the cross-linker concentration. This was rationalized as a change in permeation mechanism to that of a solution-diffusion-controlled process. A transition from porous to solu-

tion-diffusion transport is consistent with the water permeation results previously reported by Chen[46] and Wisniewski et al.[47]

The resistance to mass transfer in the stagnant fluid layer adjacent to a membrane surface is an inescapable consequence of the membrane-permeation process. Thus, during drug release from a membrane-reservoir device, drug concentration in the upstream diffusion boundary layer can be much lower than that in the adjacent drug reservoir due to the fast transport of drug across the membrane. Similarly, drug concentration in the downstream diffusion boundary layer can become much higher than the concentration in the releasing medium due to an insufficient drug removal rate. Boundary-layer effects can alter the rate, or even the kinetics, of drug release from drug delivery devices, depending on the type of device and the environment of use. The frequently observed discrepancy between *in vitro* and *in vivo* release rates can generally be attributed to this type of phenomenon. The influence of the boundary layer on the release kinetics of monolithic devices has been analyzed by Higuchi,[48,49] who used a pseudo-steady-state approach.

In the case of membrane-reservoir systems, the boundary layers offer additional resistance to mass transfer across the membrane, as if the effective membrane thickness has been increased. The steady-state release rate from such a membrane device with a saturated reservoir would therefore be reduced. Similar reduction in release rates are also expected in membrane devices with nonconstant reservoir concentration. Several approaches have been proposed in the literature, mostly in the area of membrane dialysis, to elucidate the mechanism of this boundary-layer effect and to make quantitative calculations of the true intrinsic membrane transport parameters. These proposals suggest a reduction or elimination of the boundary layer by increasing fluid turbulence (e.g., by stirring) or an estimation of the boundary-layer resistance by performing transport experiments at different membrane thicknesses or stirring speeds.

The less permeable polymer or drug selected should still provide sufficient drug-release rate to meet the therapeutic requirement. In practice, sometimes this can be difficult to achieve due to a large release-rate requirement. In this situation, compromises in membrane permeability, thickness, and area would have to be made in order to minimize the contribution of a boundary-layer effect and still maintain the desired rate of release. Aside from the material and system parameters discussed previously, other factors, such as temperature and membrane porosity, may also affect the rate of drug release.

In diffusion-controlled release systems, the transport of solute through the polymer is achieved by molecular diffusion due to concentration gradients. Depending on the molecular structure of the polymer, these systems may be classified as porous or nonporous. Porous controlled-release systems contain pores of large enough size so that diffusion of the solute is accomplished through water, which has filled the pores of the polymer. These pores are usually in the range of 200 to 500 Å. At the lower limit of this range,

hindered diffusion may occur. Therefore, correction of the solute-diffusion coefficient may have to be made to account for pore wall effects.[50,51]

Molecular diffusion occurs effectively through the whole polymer, and the solute-diffusion coefficient refers to the polymer phase. The macromolecular structure of the polymer affects solute diffusion according to theoretical analyses. Some of the polymer parameters controlling the solute-diffusion coefficient are degree of crystallinity and size of crystallites, degree of cross-linking and swelling, and the molecular weight of the polymer. Many swollen, porous polymer systems retain the main characteristics of the porous structure, so that solute diffusion occurs simultaneously through water-filled pores and through the swollen polymer per se.

In reservoir (membrane) systems, the bioactive agent is usually enclosed at relatively high concentrations between two semipermeable membranes and placed in contact with a dissolution medium (water or other biological fluid). The bioactive agent may be solvent-free or in the form of a concentrated solution. The partition coefficient describes thermodynamic rather than structural characteristics of the solute/polymer/solvent system. It is rather easy to determine experimentally, and it is a measure of solute solubility in a swollen polymer. A rigorous derivation of the partition (distribution) coefficient is presented by Lightfoot.[52]

In matrix (monolithic) systems, the bioactive agent is incorporated in the polymer phase either in dissolved or in dispersed form. Therefore, the solubility of the solute in the polymer becomes a controlling factor in the mathematical modeling of these systems. When the initial solute loading is below the solubility limit, release is achieved by simple molecular diffusion through the polymer. However, when solute loading is above the solubility limit, dissolution of the solute in the polymer becomes the limiting factor in the release process. Park et al.[37] have listed examples of diffusion-controlled reservoir and matrix devices.

D. Chemically controlled release

Chemically controlled systems include all polymeric formulations in which solute diffusion is controlled by a chemical reaction, such as the dissolution of the polymer matrix or cleavage of the drug from a polymer backbone. In most chemically controlled systems, solute release is controlled by the geometric shape of the device. Depending on the type of degradation reaction, these systems may be classified as chemically degradable (e.g., by hydrolysis) or biodegradable (e.g., by enzymatic reaction) controlled-release systems.

In chemically controlled drug delivery systems, the release of a pharmacologically active agent usually takes place in the aqueous environment by one or more of the following types of mechanisms: gradual biodegradation of a drug-containing polymer matrix, biodegradation of unstable bonds by which the drug is coupled to the polymer matrix, and diffusion of a drug from injectable and biodegradable microbeads. In contrast to mechanical and osmotic devices, the main advantages of such biodegradable systems

are the elimination of the need for their surgical removal, their small size, and potential low cost. On the other hand, all biodegradable products, as well as their metabolites, must be nontoxic, noncarcinogenic, and nonteratogenic. These requirements are not easily met and must be subject to careful scrutiny.[53]

In a system of the first type, the drug is either dispersed in the biodegradable polymer matrix or encapsulated in it, from which it is released into the surrounding biological environment by controlled rates. The particular kinetic behavior depends on the chemical composition of the polymer, the solubility of the drug in the polymer, and preparative aspects of the polymer matrix. Gradual degradation of the polymer can be facilitated by either converting an otherwise water-soluble polymer into a water-insoluble one by cross-links that are nevertheless hydrolytically or enzymatically unstable, or by using polymers that can undergo main-chain cleavage by hydrolytic or enzymatic actions. As noted previously, it is essential that none of the biodegradation products be toxic. Furthermore, all degradation products must be fully metabolized and excreted without excessive or permanent accumulation in the body. These requirements pose formidable challenges, especially when they must be combined with drug-release parameters.

E. Miscellaneous forms of controlled release

1. Ion-exchange resins

Resins are water-insoluble materials containing salt-forming groups in repeating positions on the resin chain. Ion-exchange resins have been used as drug carriers for preparing prolonged and sustained delivery by releasing the drug from the complex over approximately 8 to 12 h into the GI tract. Drug release from the complex depends on the ionic environment, such as pH or electrolyte concentration, within the GI tract as well as properties of the resin. Resin-drug complex can also increase stability of the drug by protecting the drug from hydrolysis or degradative enzymes. It also improves palatability of the formulation.

A drug-resin complex is prepared by mixing the resin with a drug solution, either by repeated exposure of the resin to the drug in a chromatographic column or by prolonged contact of the resin with the drug in a container. The drug-resin complex is then washed and dried. Drug molecules attached to the resin are exchanged by appropriately charged ions in contact with the ion-exchange groups, and the released drug molecule diffuses out of the resin. The rate of diffusion is controlled by the area of diffusion, diffusional path length, and the amount of cross-linking agent (i.e., the rigidity of the resin). Thus, the rate of drug release can be controlled during formulation.

The release rate can be further modified by coating the drug-resin complex. Coating on the resin-drug complex can be achieved by a microencapsulation process. Different coating materials alter the release of the organic anion from the anion-resin complex, and a dramatic difference in release rate

is observed with different waxes. The amount of wax covering the surface of the drug–resin complex appears to depend on the polar character of the wax. Coated and uncoated drug-resin complexes can be mixed and filled into capsules with excipients or suspended in a palatable, flavored vehicle containing suitable suspending agents. The release of drug from uncoated resin beads is expected to begin immediately, while release from the coated form begins slowly, depending on the type and thickness of coat. Mixing the coated and uncoated drug-resin complexes in suitable ratios is a reliable technique for obtaining desired release profiles.

Based on the observation that amines are released slowly from ion-exchange resins, polystyrol resins have been tried for oral depot preparations of alkaloids, such as ephedrine and amphetamine. The release rate is best prolonged if only partly alkaline exchange resins are used and if a mixture of alkaloid base and an alkaloid salt is employed. Thus, the initial phase is reduced and the continuing release of the drug is prolonged. However, the release rate depends upon pH and electrolyte concentration in the GI tract, which is higher in the stomach and declines during transit through the small intestine. Both cationic exchangers, as well as anionic exchangers for alkaline and acidic compounds, respectively, are used. Resinates and resin salts are soluble in water or in intestinal fluids and are not degraded by intestinal enzymes. Although the drug is released according to the ionic environment, it is difficult to regulate the rate of release. Disadvantages of ion-exchange resins for depot preparations are that only ionized drugs can be used and binding capacity is limited. Thus, only relatively small amounts of drugs can be bound per tablet.

2. *Altered density: Drug-coated micropellets*

Empty globular shells, which have an apparent density lower than that of gastric juice, can be used as carriers of drugs for sustained-release purposes. Conventional gelatin capsules, polystyrol, and poprice are all candidates as carriers. The surface of one of the empty shells is undercoated with a polymeric material, such as cellulose acetate phthalate, acrylic and methacrylic copolymer, or sugar. This undercoated shell is further coated with a drug–polymer mixture and any polymeric material that shows dissolution-controlled drug release (e.g., ethylcellulose, hydroxypropylcellulose, or cornstarch).[54]

This type of carrier floats on the gastric juice for an extended period while slowly releasing the drug. This same principle can be applied to formulate buoyant capsules. The particles of a drug–hydrocolloid mixture will swell to form a soft gelatinous mass on the surface when in contact with gastric juice. This somewhat enlarged particle has a density less than one and floats on stomach chyme, where it releases the drug. *In vitro* dissolution studies with this formulation show a good correlation with plasma concentration levels for chlordiazepoxide. Hydrocolloids that are suitable for this purpose are alginate, hydroxyalkylcellulose, carboxymethylcellulose, carra-

geenan, guar gum, agar, gum arabic, gum karaya, gum tragacanth, locust bean gum, pectin, and the like.

It has been reported that multiple-unit formulations have an advantage over single-unit preparations in that subunits of the multiple-unit formulation are distributed throughout the GI tract, and their transport is less affected by transit time of food. Specific density of the subunits of the multiple-unit dose is reported to significantly influence the average transit time of the subunits through the GI tract. An increase in density from 1.0 to 1.6 extended the average transit time from 7 to 25 h. The pellets are dispersed throughout the small intestine at a rate that depends predominantly on their density. Barium sulfate, zinc oxide, titanium dioxide, and iron powder are the substances used to increase pellet density. Density of the pellets must exceed that of the normal stomach contents and should therefore be at least 1.4. Moreover, a diameter of 1.5 mm is considered maximal for a true multiple-unit formulation. The drug can be coated on a heavy core or mixed with heavy inert materials, and the weighted pellet can be covered with a diffusion-controlling membrane.[55]

3. *pH-independent formulations*

When a drug formulation is administered orally, it encounters several pH environments until absorbed or excreted. If the formulation is chewed, the first environment will be pH 7. The drug will then be exposed to a pH of 1 to 4 in the stomach, depending on the amount and type of food, followed by a pH of 5 to 7 in the intestine. Many reports show a pH dependency of drug release from a sustained-release formulation. For example, the release of papaverine[56] from a commercial sustained-release preparation is significantly affected by pH of the dissolution media. Most of the drug is released in the stomach from this preparation and little is released in the intestine due to low solubility in the small bowel. Release of the drug from polymeric films has also been shown to depend on external fluid pH and not film thickness.

To achieve pH-independent drug release, buffers can be added to the drug to help maintain a constant pH. Salts of phosphoric acid, phthalic acid, citric acid, tartaric acid, or amino acids are preferred because of physiological acceptability. The rate of availability of propoxyphene after administration of a buffered controlled-release formulation showed significantly increased reproducibility, probably due to lower sensitivity of its release rate to the surrounding pH.[57]

4. *Pro-drugs*

A pro-drug is a compound resulting from chemical modification of a pharmacologically active compound, which will liberate the active compound *in vivo* due to enzymatic or hydrolytic cleavage. The primary purpose of employing a pro-drug is to increase intestinal absorption or to reduce local side effects (e.g., aspirin irritation). On this basis, one does not generally classify a pro-drug as a sustained-release mechanism. However, the ability

to reversibly modify the physicochemical properties of a drug allows better intestinal transport properties and, hence, influences the blood–drug concentration-time profile. Thus, pro-drugs can be used to improve strategies for controlled release and, in a limited sense, can be sustaining in their own right.

A water-soluble derivative of a water-insoluble drug can be developed to be a substrate for enzymes in the surface coat of the brush border region of the microvillus membrane. The water-soluble derivative becomes insoluble with a high membrane-water partition coefficient just prior to reaching the membrane. Improved blood levels by orders of magnitude for water-insoluble drugs have been reported.[57,58]

If a pro-drug has less water solubility, and hence a slower dissolution rate in aqueous fluid than the parent drug, appearance of the parent drug in the body is slowed because the dissolution process would be rate-limiting. In fact, the dissolution rate of 7,7′-succinylditheophylline is 35 times slower than that of theophylline under the same conditions, and its dissolution rate is independent of pH within the physiological pH range. Many derivatives of aspirin have been made to reduce gastric irritation, rather than to increase its absorption.

5. *Barrier coating*

The barrier-coating principle can be applied to beads, granules, or a whole tablet. If barrier-coated beads or granules are used, one portion is usually left uncoated for the immediate dosage form, while others are coated differentially in order to acquire different release patterns. Release of drug depends upon degradation or moisture-induced permeability of the coat, which is dependent on its composition and thickness. If coated granules are used for compression, care must be taken that the coating does not fracture during compression. The release mechanism is generally by dialysis, since water-insoluble but permeable plastics are used for coatings. Only in rare cases does release follow degradation. This occurs where waxes, such as beeswax, or fats and fatty acid esters, such as glycerine monostearate, are used. Within this group, the technique of microencapsulation also belongs.

Previously used film-forming or coating materials often lacked programmable release characteristics since they frequently disintegrated or dissolved upon exposure to GI fluids. The development of lacquer materials of well-defined permeability, based on methacrylate, has led to the development of suitable barrier-coating dosage forms. The barrier-coating principle can only be employed for water-soluble drugs.[59]

When plastic material, which is insoluble and undigestible in GI fluids, is used, release of drug depends on the solubility of the drug, the size and number of pores in the membrane, and the thickness of the membrane. A constant release of drug can be expected when water forms a saturated solution within the tablet, leading to drug dissolution. The tablet case, filled with water, will pass through the intestinal tract unchanged and will finally be eliminated in the feces.

By varying the functional groups of acrylic resins (Eudragit L, Eudragit S), coatings are obtained with solubility and permeability characteristics independent of pH (2 to 8). These resins possess identical properties for the pH range found in the GI tract. Thus, drug release of the active ingredient is independent of the position of the drug in the tract. Following a short period of swelling, drug liberation follows zero-order kinetics until 80–90% of the drug is released.[60]

Prolonged action of oral dosage forms based on the barrier-coating principle can be prepared by the following methods: simple film-coating of the tablet, simple film-coating of pellets or granules and filling into gelatin capsules, and compression to tablets of approximately 80% of total volume of the tablet or barrier-coated particles with approximately 20% of a filler. Even if the coatings are opened by cracks during compression, new diffusing cells are formed by fusion of the remaining film-coated particles.[61]

6. *Embedment in slowly eroding matrix*

In embedding, the active ingredients are dissolved or suspended in a mixture of fats and waxes, such as beeswax, carnauba wax, hydrated fats, synthetic waxes, butyl stearate, stearic acid, saccharose monostearate, saccharose distearate, or in mixtures of glycerine monostearate, castor oil, etc. The melt is either dispersed by spray congealing, or the solidified drug-vehicle mass is ground or milled to a proper particle size. The granules obtained are either filled into hard gelatin capsules or compressed to tablets. For retard preparations, one part of the active ingredient is formed in a normal granulate with a vehicle that disintegrates rapidly, and the rest of the active ingredient is embedded into the fat vehicle. The two different types of granules are then mixed and filled into capsules or compressed. It is also possible to form a sandwich-like tablet by compressing the embedment granules into one layer and the rapid-disintegrating granulate into a second layer on the top of the first.

Liberation of the drug from its embedment depot is by gradual erosion of the fat granules. Enzymes and pH can be of great influence by hydrolyzing the fatty acid esters, depending on the type of vehicle substance. If the esters are hydrolyzable, drug release from fat-embedded dosage forms runs parallel to the hydrolysis of the glycerides. If digestible or partly digestible fats and waxes are used, individual variations in drug release from fat-embedment dosage forms can be assumed to be high due to individual differences in pH and enzyme patterns.[62,63]

7. *Embedment in plastic matrix*

Skeleton-type preparations are made by granulating the active ingredients with inert plastic material. Several possibilities exist, including: the drug powder can be mixed and kneaded with a solution of the same plastic material in an organic solvent and then granulated or a solid–solid solution of the drug in plastic particles may be produced by dissolving the drug in

the plastic-containing organic solvent and granulating it. After the solvent evaporates, a solid–solid solution of the drug in plastic particles is produced. The granules are then compressed into tablets.

Liberation of the active ingredient from this dosage form is by leaching from the inert plastic skeleton or matrix. Only water-soluble or fairly soluble drugs can therefore be used for this procedure. The plastic skeleton retains its shape throughout transit through the GI tract and is excreted in its original shape in the feces. Drug liberation depends solely on its solubility in GI fluids and is completely independent of pH, enzyme activity, concentration, or GI motility.

A certain amount of drug is released immediately upon administration. This is the drug that is on the surface of the dosage form and can therefore be dissolved immediately. Further release depends on the penetration of GI fluid into the pores of the skeleton. If an increased amount of the active ingredient is required for the initial phase, then the manufacture of double-layer, or sandwich, tablets is indicated. Here, one layer contains the rapidly disintegrating initial phase only, while the second layer contains the skeleton of the depot phase. Skeleton tablets can also be used as cores for compressed-coated or sugar-coated tablets, for which they contain the initial phase in the coat. Disadvantages of plastic matrix tablets are that slightly soluble or insoluble drugs cannot be released from this type of dosage form.[64,65]

8. Repeat action

Repeat-action preparations contain two doses, one of which is released immediately upon administration, followed by a second dose, which is not a depot phase as discussed previously, but is a dose that is released after a certain time interval or in a certain environment. This is achieved by using enteric coating for the second dose. The second dose, which is a repeat dose, is a normal tablet coated by an enteric film. The initial phase is administered around the core in the form of a sugar coat or by compression coating.

9. Hydrophilic matrix

Oral retard preparations based on the hydrophilic-matrix principle are prepared by mixing the active ingredients with nondigestible hydrophilic gums and compressing the mixture into tablets. Upon administration, a rapid dissolution of the drug from the surface of the tablet is usually observed. When hydration and gelation of the gum at the tablet/liquid interface progresses, a viscous gel barrier is formed. The drug in this gelated form is then released at a much slower rate. The release rate of the drug is markedly influenced by the percentage and type of gum used. Liberation rate also depends on the physical and chemical properties of the active ingredient. A prerequisite for this type of dosage form is high solubility of the active ingredient. The gums used are sodium carboxymethylcellulose and hydroxypropylmethylcellulose.

Drug release *in vitro* follows a constant or zero-order release. Both inter- and intrasubject variations in *in vivo*-absorption kinetics have been found in

studies with prolonged-release dosage forms containing aspirin in a hydrophilic gelating agent. Following a lag time, individual absorption data were found to follow first-order kinetics in most instances. Using averaged data, a zero-order plot for absorption was obtained. Levy and Hollister[66] have warned of erroneous conclusions from average data if all or the majority of individual data can not be fitted satisfactorily to the model. Investigating the factors controlling the rate of drug release from hydrophilic matrices indicates that release is controlled more by drug diffusibility than by dissolution of polymer and water penetrability. As long as the integrity of the hydrated polymer is maintained, the release of drug is diffusion-controlled.

10. Polymer resin beads

Using epoxy resins, drugs can be incorporated into the plastic material, either by dissolving or suspending the active ingredient in the liquid plastic monomer. The solution or suspension is then dispersed in a hydrophilic or lipophilic medium, producing an emulsion. The bead size of the plastic monomer depends on the agitation intensity, surface tension, and degree of incorporation of protective colloids. Polymerization occurs upon heating the mixture to 50 to 60°C, and the liquid plastic droplets solidify within 2 to 4 hours to form beads.

Epoxy compounds cured with primary amines dissolve in strong acidic buffers and may, therefore, liberate the drug in the stomach. Epoxy compounds cured with acids dissolve in weakly acidic or neutral mediums and therefore release the drug in the intestine only. Resins containing the active ingredients can be obtained in bulk as well as in bead form. Dissolution rate is enhanced with an increased concentration of 2-amino-2-ethyl-1,3-propandiol in the epoxy resin. Low concentrations of chloramphenicol in such polymerization resins have no effect on dissolution rate. However, dissolution rate decreases with increasing concentration of chloramphenicol core in the form of a sugar coat or by compression coating.

The *in vitro* release of chloramphenicol from different bead polymers containing methyl methacrylate and α-methacrylic acid in various buffer solutions was found to depend on the amount of α-methacrylic acid content in the polymer and the bead particle size. Plastic polymer beads may also be formed by extrusion molding. Polymers, being solid and brittle at room temperature but liquefying at higher temperatures, are suitable for extrusion molding. For preparation, a free-flowing solid mixture of drug and thermoplastic material is melted at 100 to 110°C and injected into cooled metal molds. Polymers between drug and epoxy-amine resins are soluble in an acidic environment (initial phase), whereas polymers between drug and vinyl acetate and crotonic acid are soluble in a slightly acidic and neutral environment (depot phase).[67]

11. Passage-sponge formation

A new method to obtain depot preparations has been described. Soft gelatin capsules can be prepared by dissolving or suspending the active ingredients

in a polyethylene glycol solution of shellac or polyvinyl acetate. Additional vehicle substances, such as stearates, acids, bases, or phosphates, may be added. The filling material is then incorporated into a gelatin solution for the manufacture of soft gelatin capsules by the usual method. The gelatin goes into solution in the aqueous gastrointestinal fluids. The interior of the capsule becomes spongelike due to the penetration of the aqueous media into the capsule from the surface. Finally, the whole interior is converted into a spongelike skeleton as the aqueous medium penetrates deeper into the capsule. The active ingredient is released from this microporous sponge by diffusion. Since the sponge-like wall is quite thin at the beginning, a large amount of drug is liberated during the initial phase. Usually, about 30 to 40% of the drug content is released within the first hour. Further drug release follows continuously and is complete after approximately six hours.

Another new method of preparing depot dosage forms based on the passage-sponge formation uses a soluble alginate (sodium alginate) and a calcium ion donator ($CaHPO_3$) with other vehicles. The dry mixture of these substances and a solid drug are compressed into tablets. Upon administration, a spongelike matrix is formed under the influence of the GI fluids, from which the drug is released by dissolution and diffusion. The sponge is formed progressively from the outside to the inside of the tablet. The GI fluid dissolves the alginate and the calcium compound. The alginate and calcium ions react immediately with each other, forming a spongelike layer of calcium alginate.[68]

12. Drug complex formation

Depot preparations can be made with drugs having an amine group in the molecule. Examples of these are alkaloids, antihistamines, and amphetamine, which can be complexed with tannic acid. An alcoholic solution of the amine and the tannic acid is combined, and the precipitated complex is washed, dried, and mixed with additional vehicles and either compressed into tablets or granulated and filled into capsules. A preparation of methylcellulose salts of basic amines is also possible for this type of formulation. Usually, the solubility of the complex is greatest at acidic pH. Therefore, other vehicle substances, such as buffers or hydrophilic gums, are added to prevent too rapid dissolution. The different groups of oral prolonged-action dosage forms, their manufacturing characteristics, and drug release characteristics are listed by Cavallito et al. and Ritschel.[69,70]

13. Bioadhesives

One of the simplest concepts for prolonging the duration of drug presence in the GI tract and localizing it in a specific region involves binding the product to the mucin/epithelial surface of the GI tract. This is the premise of bioadhesion. Although the concept is old, it is receiving renewed attention because of a better understanding of polymers and the GI tract. To this end, it is now possible to attach a number of polymeric substances noncovalently

to mucous tissue and keep them localized for an extended period of time. One of the early researchers in this area was Nagai et al.,[71] who used the bioadhesion principle to treat aphtha, an inflammation of the mouth. He used an anti-inflammatory drug mixed with a bioadhesive polymer that would attach to the tongue or cheek and remain in place for many hours. He has since extended the clinical application of this concept to the treatment of cervical cancer and to the nasal delivery of peptides. Extended, local release of the drug has yielded good clinical results in the treatment of both aphtha and cervical cancer.

For the past decade, work at the University of Wisconsin, School of Pharmacy, has been directed to understanding the mechanisms of bioadhesion and controlling them for drug delivery purposes. Experimental work at Wisconsin, with drugs in the eye and GI tract, has led to once-daily administration and uncovered a number of other advantages, including improved duration of blood or local drug levels, improved fraction of dose absorbed, improved local drug targeting, strategies for drug–polymer pro-drugs, platforms for enzyme inhibition (peptidases), and membrane permeability for enzyme change in a restricted area.

One of the great potential advantages of an oral bioadhesive is in its use with peptide drugs. Protein and polypeptide drugs, which are expected to increase substantially in number as a result of genetic engineering, are subject to peptidase inactivation in the GI tract and commonly have difficulty crossing the intestinal barrier because of their size.[70] To overcome these concerns, it is necessary to localize a dosage form in a specified region of the GI tract to inhibit local peptidase activity and perhaps modify intestinal membrane permeability. Bioadhesives offer the potential to partially accomplish this goal and also offer the best and most significant opportunity to improve controlled oral delivery.

14. Local, targeted systems

An effort is being made to find specific binding sites in the GI tract to which drugs can be targeted. Knowing there is a specific sugar-binding site at a specific region of the intestine could, for example, conceivably permit attachment of a drug to that sugar and possibly achieve localization. In a similar manner, small peptides, such as fibronectin fragments, can bind to epithelial cells, and might be good platforms for drug delivery. These studies seem further from commercialization than the more physical systems described earlier, but they have considerable potential to target drugs to specific locations.[72,73]

15. Synchron system

The Synchron system is Forest Laboratories' patented procedure based on the blending of cellulose and noncellulose material with a drug. These materials are combined into a homogeneous mixture from which tablets are made. When the Synchron system tablet comes in contact with water, the outer

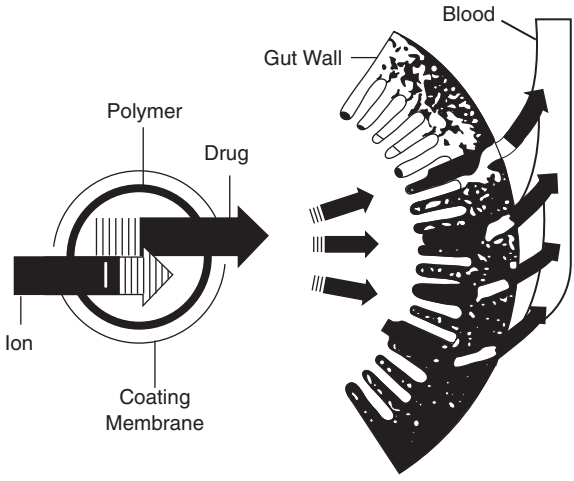

Figure 5.2 Schematic drawing of a Pennkinetic system.

layer of the matrix softens to a gel-like consistency, which allows the trapped drug to release at a controlled rate. The simplicity of this system allows the completion of a desired drug formulation within a matter of months. Forest has marketed Theochron, a controlled-release theophylline product using the Synchron system (see Figure 5.2).

16. Pennkinetic and other liquid controlled-release systems

The Pennkinetic system is Pennwalt's proprietary liquid system, which makes use of two controlled-release technologies: ion exchange and membrane diffusion control. The Pennkinetic system is formed by reacting a drug in its ionic state with a suitable polymer matrix. This polymer-drug complex is then subjected to polyethylene glycol 4000, which imparts plasticity and stability to the complex. A coating of ethylcellulose is applied by air to the preparation to form a water-insoluble but ionic and drug-permeable coating. To be effective, this system requires that a drug interact ionically with the ion-exchange polymer.

Since the ion concentration in the human GI tract is remarkably consistent, medication release from the Pennkinetic system is quite precise and unaffected by variations in pH, temperature, or contents in the stomach or intestine. Pennwalt has used this system in making a variety of long-lasting nonprescription drug products. Its first product was Delsym, a 12-h cough product containing dextromethorphan. Pennwalt also introduced 12-h cold preparations called Corsym and Cold Factor 12, which employ the same delivery system to supply chlorpheniramine and phenylpropanolamine, respectively.

In addition to prolonged, precise release of medication, the Pennkinetic matrix system makes the drug tasteless, which is helpful in masking the bitter taste of many drugs, especially in pediatric formulations. Elan Corpo-

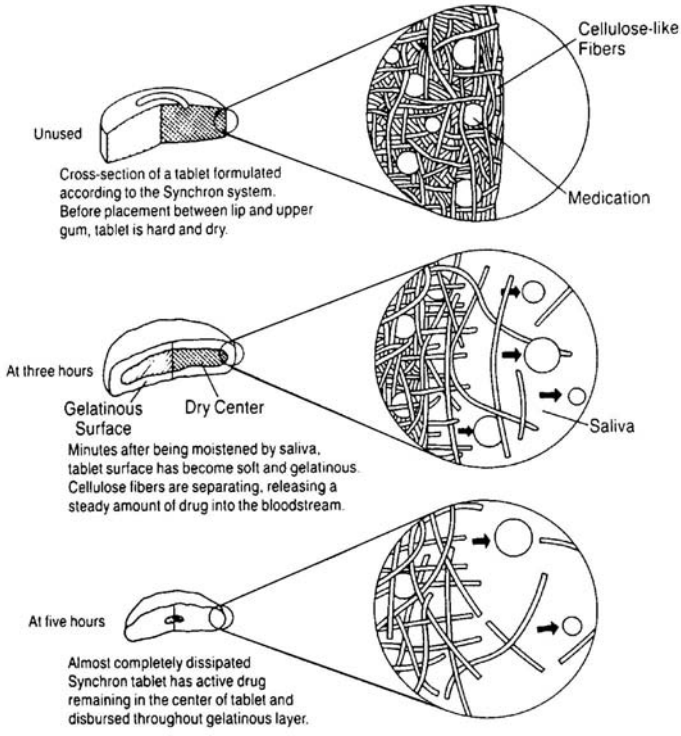

Figure 5.3 The Synchron tablet-release mechanism. (From *Pharm. Tech.*, The Latest Developments in Drug Delivery Systems, Conf. Proc., Oct. 1985, 31. With permission.)

ration has also developed a liquid sustained-release system called Pharmazome. While the company has not disclosed the mechanism of action of this system, it is believed to provide the same benefits of long action and taste masking offered by the Pennkinetic system (see Figure 5.3).

17. Controlled-release capsules

While drugstore shelves are full of many ethical and proprietary preparations of conventional and prolonged-release capsules, the introduction of pH-independent, controlled-release capsules has occurred only during the past few years. These capsule products use different technologies to achieve zero-order release of active ingredients.

Inderal LA, a prescription drug, has been introduced by Ayerst. It uses polymer-coated, controlled-diffusion technology to achieve 12-hour release of therapeutic levels of propranolol. Polymer coating used for preparing Inderal LA beads gives the drug higher than normal density of 1.1 to 1.3. Higher-density formulation helps keep the drug in the upper alimentary canal for a substantially longer time.

Searle's Theo-24 was the first 24-hour theophylline therapy on the market. Theo-24 uses a chemical timing complex to produce very small theo-

phylline-coated beads that provide dependable, zero-order controlled drug release. A tiny sphere of sugar and starch forms the core of the bead. The core is first coated with theophylline and then with a timing complex. The resulting beads are put into capsules for oral administration. When the capsule dissolves in the GI tract, the timing coating on the bead, which is insoluble, slowly erodes. The drug, which is highly soluble, moves through the coating into the GI tract. In the core, the starch swells and pushes the drug out, while the dissolving sugar also helps carry the drug through the chemical timing complex. This results in a constant release.

When the Theo-24 capsule dissolves, many tiny beads are widely dispersed throughout the GI tract and there is a more even distribution of the drug than would otherwise be achieved with a tablet. Because of this dispersion, the beads are less affected than a single tablet would be by variations in stomach-emptying time and rate of movement through the intestine. The dispersion of the beads also helps to overcome the potential problem of localized high concentration of drugs that can irritate the gastric mucosa.

Burroughs Wellcome Co. introduced Lanoxicaps, a new form of digoxin in a soft elastic gelatin (SEG) sustained-release capsule formulated by R.P. Scherer Company. Scherer's sustained-release SEG capsule is a controlled-release delivery system embodying a unique matrix. The matrix allows the drug to diffuse out of the capsule, providing a constant level of drug in the blood over a period of 12 h. Digoxin therapy with Lanoxicaps allows digoxin to be much more rapidly and completely absorbed. Whereas digoxin tablet bioavailability is only in the range of 60 to 80%, bioavailability with Lanoxicaps is similar to that following IV administration (greater than 90%).

18. Controlled-release tablets

The wax-matrix delivery system employs a tablet made up of a honeycomb-type of wax matrix. As the tablet passes through the GI tract, the active ingredient is slowly released from the matrix and is absorbed in the body. Ciba-Geigy's Slow-K (potassium chloride) tablet uses a wax matrix. Ciba-Geigy has also introduced a slow iron tablet in a wax matrix called Slow-Fe. While Slow-K is widely used and Slow-Fe is well accepted, some recent studies have shown that Slow-K matrix tablets tend to cause more gastric irritation than the microencapsulated Micro-K.

Theo-Dur tablets use Key Pharmaceutical's patented controlled-release tablet formulation to achieve zero-order drug availability. Unlike Theo-24, Theo-Dur requires 12-h dosing. However, Theo-Dur was on the market long before Theo-24 and still leads the theophylline market in sales.

Unlike conventional tablets, buccal or transmucosal tablets pass directly into the bloodstream through the oral mucosa. This avoids liver extraction, which occurs with orally administered drugs. Buccal tablets are not swallowed but are kept in the buccal pouch between the cheeks and the gum. They are dissolved rapidly in the mouth. Merrell-Dow's Susadrin tablets are buccal tablets that use Forest Lab's Synchron system to release nitroglycerine

in a controlled manner over a period of 6 hours. Zetachron Co. also has a buccal delivery system for nitroglycerine.

19. Hoffmann-La Roche's Web Delivery System

Hoffmann-La Roche owns a series of patents on a high-tech drug delivery system called Web Delivery System (WDS). The Web Delivery System consists of an edible web formed by paperlike polymeric material on which a drug is deposited in suspension or powder form. The coated drug webs are then laminated to produce a multilayered structure of 6 to 20 layers. The WDS system uses a number of drug-release mechanisms, such as diffusion, disintegration, and erosion, to achieve controlled release of active ingredients at a desirable rate. Roche has used this system to prepare oral dosage forms for benzodiazepines and digoxin. However, none of these products have yet been marketed.

20. Hydrodynamic cushion system

Elan Corporation has developed an oral solid dosage form using a cushioned material. This cushioned material allows drug-bearing granules to be compressed into a unique tablet. Unlike conventional tablets, this tablet is made from cushioned material that breaks apart immediately after entering the GI tract and releases drug granules for controlled release. According to Elan, incorporation of the cushion material allows more active ingredients per dose and is cheaper to produce.

21. Floating delivery system

The 3M Company has developed an oral dosage form in which the drug-carrying matrix is covered on either side by a bubble-type barrier film. The barrier layer causes the tablet to float. The matrix layer releases the drug in zero-order fashion in the stomach. This system has been used to deliver theophylline.

22. Meter release system

This is a controlled-release drug delivery system developed by KV Pharmaceutical Company. It consists of beads or granules coated with a rate-controlling membrane system specific for each drug compound. This flexibility of rate-controlled membrane system allows precise control of drug-release rates. The meter release system has been used for preparing a long-acting capsule form of Actifed®. It has also been used for many other compounds, including antihistamines and cardiovascular agents.

23. Hydrodynamically Balanced System

Hoffmann-La Roche has developed a patented oral drug delivery system called Hydrodynamically Balanced System (HBS). It contains one or more active ingredients combined with a hydrocolloid in such a way that the entire formulation becomes hydrodynamically balanced. When the formulation

enters the gastric fluid, it acquires a specific gravity of less than 1. Low specific gravity allows it to become buoyant in this fluid, and it stays in the stomach for a prolonged period until all of the active ingredients are released. This system is especially useful for drugs that are absorbed in the upper portion of the duodenum, undergoing abrupt changes in solubility in different pH media, intended to act in the stomach contents, and likely to cause gastric irritation. Roche's controlled-release form of Valium®, called Valrelease®, is a good example of this system.

24. Other oral controlled drug delivery systems

Avitek has an exclusive licensing agreement from Yissum for an innovative submicronized fat-emulsion drug delivery system (SES formula) for oral or parenteral administration. It is expected that stable emulsions of certain drugs will improve efficacy and reduce side effects. Preclinical studies with diazepam have been successfully performed, and work is now underway with other compounds.[74]

Destab is a broad line of more than 14 directly compressible tablet excipients prepared by Desmo Chemical (KV). The products are designed for tablet formulations in which optimal compression or flow characteristics are desired. The technology has been extended to incorporate active ingredients, including paracetamol, niacinamide, riboflavin, thiamin, and various minerals. Descote is a delivery system for encapsulating small-particle vitamins, minerals, and pharmaceutical chemicals by the same company. It provides superior taste masking, improved stability profiles, and homogeneous particles of combinations of materials. A broad line of Descote B vitamins, ferrous fumarate, potassium chloride, paracetamol, zinc gluconate, copper gluconate, ascorbic acid, magnesium oxide, ferrous lactate, and many other vitamins and minerals are currently available.

Pharmedix (IVAX) has developed a granular drug delivery system for use with certain ethical and OTC products. The drug is incorporated into granules, each of which is a microencapsulated delivery system. They can be administered either by sprinkling the granules from a premeasured capsule onto food or directly into the mouth, by swallowing a capsule containing the granules or suspending the granules in water. The delivery system results in improved therapeutic characteristics of the drug and a more convenient mode of administration.[74]

Elan has developed a new delivery system for the oral administration of highly insoluble drugs. INDAS (insoluble drug absorption system) is currently being applied to certain dihydropyridine compounds and is further being used in a range of insoluble compounds from various therapeutic classes. To date, it has enabled the development of once-daily formulations of isradipine, nicardipine, nifedipine, and a formulation of hydergine. This new tabletting technique has proven to be highly suitable in the development of long acting tablets with excellent bioavailability for highly insoluble drugs and other problem compounds.[74]

Gacell Laboratories has reported on the firm's Multipor controlled-release technology. Tablets prepared using this technology have a porous outer membrane composed of a water-insoluble polymer and a soluble pore-forming substance. When exposed to gastric fluid, the pore-forming substance dissolves, which allows the fluid to penetrate into the tablet core as the drug diffuses outward at a constant rate. According to the manufacturer, the technology allows for the controlled release of drugs independent of pH values, peristaltic movements, and intake of food and water. In addition, the outer membrane protects patients from GI irritation, masks unpleasant tastes, and makes the tablets easy to swallow. This technology can be applied to tablets of various shapes, colors, and sizes, and the outer coating can accept printed text or trademarks.[74]

Biotechnology Australia is investigating an oral delivery system for drugs, hormones, and vaccines by linking them to vitamin B-12. Vitamin B-12 is rapidly absorbed from the gut via a receptor for intrinsic factor (IF), a naturally occurring protein that complexes with vitamin B-12. Thus, substances that can be coupled to vitamin B-12 in a way that does not affect the formation of the receptor-IF-vitamin B-12 complex or its subsequent absorption are potential candidates for this method of oral delivery.[74]

Benzon is developing a multiple-unit, controlled-release tablet formulation of propranolol using its Repro-Dose technology. The formulation is unique in that it is a multiple-unit tablet using a water-based, diffusion-coating system.[74]

Elan has recently announced the production of Asprilan Retard, containing aspirin, and Elangesic Tablets, containing ibuprofen. These formulations were made using SODAS (solid oral drug absorption system).

The first potassium tablet to deliver 20 mEq of potassium (twice the amount in other potassium tablets) was developed by Key Pharmaceuticals. The product, K-Dur 20, utilizes a patented microburst release system and is indicated for prevention and treatment of hypokalemia. K-Dur 20's high-tech system is said to give the product a high safety profile, sparing patients from many of the side effects of conventional potassium medications. Like a liquid, K-Dur 20 is designed to disperse immediately, distributing minute sustained-action particles over a wide surface in the stomach. As a result of its delivery system, K-Dur 20 minimizes contact between concentrated quantities of potassium and the lining of the GI tract, thereby reducing the risk of gastric irritation.[74]

KV Pharmaceuticals has developed a drug delivery system that allows unpalatable solid drug particles to be combined with liquids and taken orally in a taste-free manner. Marketed under the trade name Liquette®, it consists of a solid dispersion of the active drug in an inert, biodegradable, particulate matrix. The delivery system allows larger volume doses of solid drugs to be administered and allows the rate of release of the active drug to be controlled in order to reduce GI irritation or to prolong drug absorption. Two or more drugs can be incorporated simultaneously in the Liquette particles, which can be coated to provide additional control of drug release, enhanced drug

stability, uniform suspension of the particles in liquids, and alteration of GI transit time, thus enhancing bioavailability.[74]

Micro-Release is a long-acting delivery system developed by KV Pharmaceutical Co. The finished products are in the form of minispheres of encapsulated particles, with the active ingredient contained in a biochemically matched matrix. Sphere diameters vary from 100 to 500 μm and are suitable for use in encapsulated, tableted, or bulk form. Variation in matrix components provides a wide range of both rate and duration of release (including once-daily dosing) throughout the GI tract and protection from moisture, pH effects, and enzymatic dissolution. Micro-Release products are claimed to offer such benefits as effective utilization of the product and improved content uniformity.[74]

VI. Survey of oral controlled-release products

(Brand names are in parentheses)

Acetazoamide (Diamox Sequels)
Disopyramide (Norpace CR)
Isosorbide dinitrate (Isordil)
Nitroglycerine (Nitrospan, Nitrobid)
Papaverine HCl (Pavacen Cenules)
Pentaerythritol tetranitrate (Pentraspan SR)
Propranol (Inderal LA)
Quinidine sulfate (Quinidex Extentabs)
Quinidine gluconate (Quinaglute)
Verapamil (Isoptin SR, Calan SR)
Aspirin (Measurin)
Chlorpromazine (Thorazine Spansules)
Dextroamphetamine sulfate (Dexedrine Spansules)
Diazepam (Valrelease)
Diethylpropion HCl (Tenuate Dospan)
Fluphenazine HCl (Permitil Chronotabs)
Indomethacin (Indocin SR)
Lithium (Lithobid)
Meprobamate (Meprospan)
Methamphetamine HCl (Desoxyn Gradumets)
Methylphenidate HCl (RitalinSR)
Morphine sulfate (RoxanolSR)
Ophenadrine citrate (Norflex)
Phenylpropanolamine HCL (Acutrim, Dexatrim)
Prochlorperazine (Compazine Spansules)
Hexocyclium (Tral Gradumets)
Clinoril (Sulindac)
Aminophylline (Phyllcontin)
Antitussive combinstions (Rescap, Ornade Spansules)

Brompheniramine maleate (Bromphen, Dimtane)
Chlorpheniramine maleate (Chlor-Trimeton)
Decongestant and antihistamine (ResaidSR, NovafedSR Dristan)
Decongestant, antihistamine, and anticholinergic (Dallergy, Supres)
Pseudoephedrine HCl (SudafedSA)
Theophylline (Gyrocaps, Theo-24, Theobid, Theovent)
Trimeprazine (Temaril Spansules)
Tripelennamine (PBZ-SR)
Xanthine combinations (Isofil, TedralSA)
Ascorbic acid (Ascorbicap, Cevi-Bid)
Ferrous sulfate (Mol-Iron, Filmtabs Feosol Spansules)
Nicotinic acid (Nicobid, Nico-400)
Potassium (Micro-K, Slow-K, Klotrix)
Vitamin combinations (NeoVicaps)
Naproxen (Naprosyn)
Procainamide HCl (ProcanSR, PronestlySR)
Lanoxin (Lanoxicaps)
Iron (Slow-Fe)
Metoprolol (Lopressor)
Salbutamol (Volmax, Ventolon)
GITS-Nifedipine (Procardia)
GITS-Prazosin (Minipress)
Vitamin C (AcuSystem C)
Methyldopa (Elanpres)
Ibuprofen (Motrin)
Diltiazem (Cardizem)
Spironolactone (Aldactone, Aldactazide)
Thioridazine (Mellaril)
Diclofenac (Diffucap)
Acetaminophen (Paracetamol)
Cimetidine (Tagamet)

VII. Recent advances

- Anderson and Powell have synthesized enterically active microcapsules with controlled release in aqueous environments. These microcapsules exhibit rapid and relatively slow release of material in aqueous acid environments.[75]
- Rembaum has reported that ions that covalently bind to small, polymeric spheres can be used for binding anions and polyanions in separation, analytical, diagnostic, and clinical applications.[76]
- Waxlike materials have been used by Blichare et al.[77] to prepare controlled-release granules. Among the number of waxlike materials that can be used are the following: glyceryl monostearate, hydrogenated tallow, castor wax, myristyl alcohol, white beeswax, myristic

acid, stearyl alcohol, substituted monoglycerides, diglycerides, triglycerides, carnauba wax, acylated monoglycerides, and stearic acid.

- A carrier, depot, or bonding system for a drug that allows sustained release of a drug has been used by Baukal et al.[78] A wide variety of drugs can be used with the carrier to produce a dosage form that can be administered orally, externally, or by implantation. The carrier material consists of physiologically innocuous, inorganic, or organic materials that are totally or almost totally nonabsorbable in the body. For its properties as a carrier of active pharmaceutical substances, what is decisive is the special porous structure. It consists of "inkwell pores" (i.e., it contains cavities connected to the outer surface of the bonding substance by narrow passages (pore necks)). The drug is embedded in the cavities.
- A process for preparing tablets containing microcapsules without rupture of the microcapsules has been prepared by Estevenel et al.[79] These tablets contain a number of superposed layers, of which the medial layer is essentially constituted of microcapsules containing an active substance. The exterior layers, which may possibly also contain identical or different active substance and which have a composition usual for the formulation of tablets, constitute means of protecting the microcapsules of the medial layer, particularly against compression shock.
- Gastric-resistant gelatin capsules having two coatings have been described by Leiberich et al.[80] The capsules are characterized by a gastric juice-resistant outer layer consisting of an anionic polymerizate of methacrylic acid and acrylic acid esters. They also contain an intermediate layer consisting of a cationic polymerizate of di-lower alkylamino-lower alkylmethacrylate with other neutral methacrylic acid esters between this outer layer and the gelatin shell.
- Capsules that are completely dissolved, or slurried, within short periods of time have been developed by Controulis et al.[81] The capsule shell is apertured, and the holes are covered by a water-soluble barrier film that seals the holes and blocks any escape of the contents from the shell. The film is more water-soluble than the cap and the body parts of the shell so that when the package is contacted with water, as in the digestive tract, the film rather than the shell dissolves first, exposing the contents for dissolution or release by way of the apertures, while the shell is still intact.
- A rigid canister dispenser has been described by Higuchi and Leeper.[82] This osmotically driven fluid dispenser for use in an aqueous environment is comprised of a shape-retaining canister having controlled permeability to water; an osmotically effective solute confined in the canister, which, in solution, exhibits an osmotic pressure gradient against water in the environment; and an outlet in the canister wall. The dispenser includes a flexible bag of relatively impervious material that holds the fluid to be dispensed and is housed in the

canister with its open end in sealed contact with the canister such that the canister outlet communicates with the bag interior.

- A multizone or multilayered tablet is produced by the process described by Beringer and Woltmann.[83] The process is characterized by a nonplastic tablet and a plastic chewing gum mass. One of the masses contains at least one pharmaceutically active ingredient and is compressed to form the joined tablet. The joined tablet has at least one plastic zone comprising the chewing gum mass. The chewing gum mass contains a water-soluble portion, which, although it can be kneaded in the mouth, cannot be dissolved or chewed.
- The process developed by Michaelis[84] provides a method of preparing improved controlled gastric-residence formulations that involves treating the polymeric film coating of such formulations with a volatile amine. Volatile amines include those which are volatile at ambient temperature, may be volatilized by raising the polymer-treatment temperature, or lowering the polymer-treatment pressure (e.g., vacuum treatment).
- Nitrofurantoin is an antibacterial agent for the treatment of urinary tract infections. The drug is remarkably well tolerated in humans. However, adverse reactions occur, including anorexia, nausea, and emesis. Numerous attempts have been made to alleviate these undesirable side effects while providing a dosage form requiring less frequent administration. Huber developed improved, pharmaceutically acceptable, layered tablets containing nitrofurantoin in sustained-release form.[85]
- It has been found that some of the more active polyene macrolides (e.g., candicidin, fungimycin, hamycin) are somewhat unstable under the acidic conditions in the stomach and cause GI irritation (i.e., emesis and diarrhea) in some patients. This has hindered achieving optimum effectiveness by the oral route. A method has been found by Gordon and Schaffner.[86] for increasing overall effectiveness, including stability and GI tolerability, of these drugs. Compositions containing a polyenic macrolide and a suitable absorbent material, preferably in bead form, are used in treating various conditions.
- Macrolide antibiotics are sparingly water-soluble substances. In orally administrable formulations, the use of an amorphous solid form, having better solubility, can lead to full effectiveness of these antibiotics. Attempts to obtain amorphous solids of macrolide antibiotics by ordinary techniques (e.g., lyophilization or the rapid cooling of a molten liquid) result in products containing crystals or products that are readily converted to crystals with the passage of time. Consequently, it is difficult to obtain crystal-free amorphous solids that are stable with the passage of time. Sato et al.[87] have succeeded in developing a process to overcome these problems.
- Erythromycin salts and esters, such as the alkylsulfate salts or the mono-alkyl erythromycin esters of dicarboxylic acids (e.g., the eryth-

romycin ethyl succinate), have enjoyed excellent acceptance due to their wide spectrum of antibacterial activity. Unfortunately, some of these esters or salts have a number of physical and chemical properties that are objectionable for administration in the form of liquid suspensions. For instance, erythromycin ethyl succinate has a bitter taste which is very difficult to mask; even worse, it is known that when exposed to an acidic environment, it eventually converts to an anhydro form that is inactive. The process described by Farhadieh[88] is designed to protect particles of erythromycin derivatives from being inactivated by the pH of the stomach and simultaneously cover their objectionable taste.

- An early method for making multilayer aspirin tablets, including a timed-release layer, has been developed by Guy and Powers.[89] Hill[90] has further described improvements in connection with several other analgesic and antipyretic tablets. APAP (N-acetyl-p-aminophenol) has long been known to be useful as an analgesic or antipyretic agent and has found its way into several commercially available products. However, the speed at which its action takes effect and the amount of it which is absorbed is less than desirable. This is at least partly due to the relatively slow rate at which it is absorbed into the bloodstream from the GI tract. Weintraub et al.[107] have devised a tablet formulation that provides improved absorption.
- A new method for preparing galenic forms able to deliver a drug with a constant rate has been described by Vergnaud et al.[91] It consists of surrounding a sphere made of drug dispersed in a polymer-matrix with a layer of Gelucire. The layer of Gelucire plays the role of a membrane, while the drug-polymer mixture provides the drug. As a result, this technique provides the drug in synthetic gastric liquid without any potential danger, the drug being dispersed in the polymer.
- Self-emulsifying systems are well known to the herbicide and pesticide industries for their advantage in the transportation of lipophilic products. The system for pharmaceutical use described by Pouton et al.[92] utilizes a vegetable oil and a nonionic surfactant, which are likely to be acceptable for oral ingestion.
- Many of the undesirable side effects associated with current oral contraceptives are dose-related. If the drug is absorbed slowly over a period of time, lower doses can be effective and side effects reduced. The objective of studies by Schlameus et al.[93] was to prepare and evaluate sustained-release oral formulations of marketed contraceptive steroids (e.g., ethynyl estradiol, norethindrone, norethindrone acetate, and mestranol). Selected formulations were tested for reduction of daily peak concentrations, body burden, and contraceptive efficacy. Evaluation of the formulations was accomplished by *in vitro* release-rate testing, selected *in vivo* studies using baboons, and clinical studies using the most promising systems.

- Theophylline ethylcellulose microcapsules, prepared by using ethylene-vinyl acetate (EVA) as a coacervation-inducing agent, have exhibited a sustained-release behavior *in vitro* that correlates well with *in vivo* bioavailability in rats. In a study by Lin and Yang,[94] the effect of compression pressure, particle size, and types of excipients used on physical parameters and dissolution properties of tablets made from theophylline ethylcellulose microcapsules have been investigated.
- A report by Chattaraj et al.[95] concerns the development of a viable microencapsulated, controlled-release drug delivery system. Microcapsules containing ranitidine, which was selected as the core material, were prepared by phase-separation coacervation of ethyl cellulose in nonaqueous solvents. The effects of different concentrations of the coacervation-inducing agent polyisobutylene on drug release were studied.
- Located throughout the GI tract of man and other mammals are distinct lympho-reticular follicles (Peyer's patches) that possess IgA precursor B cells. Subsequent to antigen sensitization, these precursor B cells migrate throughout the body and repopulate the lamina propria regions of the GI and upper respiratory tracts and differentiate into mature IgA-synthesizing plasma cells. This migration pattern provides a common mucosal immune system by continually shuttling sensitized B cells to mucosal sites for responses to gut-encountered environmental antigens and potential pathogens. To take advantage of the mucosal system, Gilley et al.[96] have developed microcapsule formulations that target Peyer's patches and release antigens at controlled rates. The microcapsules protect the antigens from degradation in the GI tract and are effectively taken up by Peyer's patches. After uptake, the microcapsules release the antigen, resulting in sensitization of precursor B cells.
- Microparticles (containing propranolol or quinidine sulfate) or nanoparticles (spray-dried latex particles) have been dispersed into aqueous solutions of ionic polysaccharides (e.g., chitosan or sodium alginate) and then mixed with aqueous solutions of suitable counterions (e.g., tripolyphosphate or calcium chloride). The ionic character of the polysaccharides allows site-specific release of the microparticles in the GI tract. Chitosan beads, which dissolve below pH 6, release the microparticles in gastric juice, while sodium alginate beads stay intact in gastric juice but rapidly disintegrate in intestinal fluids. The beads could be taken as prepared or placed into capsules.[97]
- Research by Shefer and Kost[98] have focused on the application of starch from various vegetative sources for enzymatic targeted drug delivery. Starch is commonly used as food and is known to undergo enzymatic breakdown by amylase. Starch microbeads have been produced using a concentrated emulsion (loaded with a releasing agent) treated with a strong base and a calcium chloride solution. It was found that entrapment efficiency decreases as the molecular weight

of the entrapped molecule increases. Microbeads prepared from different sources of starch undergo different breakdown rates. The release of high molecular weight molecules is due to matrix degradation, while small molecules are released by diffusion and degradation. Parameters affecting release kinetics are polymer source, molecular weight, and release environment (e.g., pH, enzymatic activity).

- Attributes of the ideal contraceptive drug delivery system include safety, efficacy, reversibility, absence of side effects, minimum steroid load, and high patient compliance. The objective of the work reported by Eldem et al.[99] was to formulate ultrafine lipid pellets as steroid carriers for oral contraception by using spray drying and congealing techniques. By taking into consideration the basic mechanism of fat absorption, physiologic lipid carriers, such as triglycerides and lecithin, were used to promote the lymphatic absorption of steroids, thus avoiding first-pass metabolism by the liver and increasing their bioavailability.
- Many hydrophilic polymers have been used in controlled-release tablet formulations, but modified starches have never been investigated extensively for this purpose. Herman and Remon[100] reported the use of starches containing different amounts of amylose and modified by spray drying, drum drying, or extrusion in controlled-release formulations. The influence of silicium dioxide and some lubricants on drug-release rate from tablets containing starch: theophylline (60:40 w/w) has been investigated. Most starches containing less than 30% amylose show a dramatic reduction in drug release. Silicium dioxide had no influence on release rate, while magnesium stearate and polyethylene glycol increase the release rate dramatically.
- A bioadhesive tablet of metronidazole has been developed for oral or vaginal administration. It was found that pH in the range of 2 to 7, although known to modify the swelling of the carbopol, had no significant effect on the bioadhesive power of the tablet in conditions of weak hydration. This was explained by the substantial difference between the time required for swelling and that required for a detachment test and also by the specific buffer capacity of carbopol. On the other hand, ionic strength had a clear effect on the bioadhesive power, which decreased with an increase in ionic strength.[101]
- An orally applicable pulsatile drug delivery system in dry-coated tablet form has been prepared using diltiazem as a model drug and a polyvinyl, chloride-hydrogenated, castor oil-polyethyleneglycol mixture as the outer shell of the tablet. *In vitro* drug release from the prepared tablet exhibited a typical pulsatile pattern with a 7-hour lag phase.[102]
- Ampicillin has been embedded in a chitosan matrix to develop an oral release dosage form. It appears that the drug forms a crystal structure

within the chitosan beads, which slowly dissolves out to the dissolution medium through the micropores of the chitosan matrix.[103,104]

- The oral delivery of O-(N-morpholino-carbonyl-3L-phenylaspartyl-L-leucinamide or (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylene, a new renin inhibitor, has been studied in an *in vivo* rat model using emulsion formulations. The components of the emulsion formulations were chosen based on their proposed effects on membrane structure, fluidity, and solute transport. The results suggest that in the intestine, the particle size of the emulsion is reduced in the presence of bile fluid while the drug resides primarily in the oil phase.[105]
- Cephalosporin has been enterically coated with an absorption-promoting excipient for oral administration. The novelty claimed for this preparation resides in a two-component absorption-enhancing agent. The first component is ethoxylated n-dodecanol, while the second component is a salt of caprylic acid.[106]
- Delayed-release osmotic devices for delivery of verapamil have been described. This involves a tablet formulation that is intended to be taken at bedtime, but that releases verapamil only in the early morning hours. A drug-containing layer was prepared with verapamil, Polynox N-750 (EO polymer), polyvinylpyrrolidone K29–32, sodium chloride, and magnesium stearate. Drug and osmotic pump layers were co-tableted and then coated with a wall-forming composition. Exit orifices were drilled on the drug-containing side of the tablet.[107]
- Nicotine has been delivered osmotically to the oral mucosa using a coated tablet that provides a readily absorbable form of nicotine *in situ*. The bitartrate salt of nicotine was tableted with sodium carbonate, PEO, HPMC, sodium saccharin, and flavorants. Nicotine tartrate exhibits good stability during storage and is readily converted to the absorbable base form in the mouth.[108]
- A Scherer dosage form, the Pulsincap, provides a dose of drug at either a predetermined time or a predetermined place in the GI tract. The system, which resembles a capsule, has a water-insoluble body that contains the active agent: either a powder or liquid. A water-soluble "cap" protects a hydrogel plug that is seated in the neck of the main compartment. Another type of Pulsincap has an enteric film coating over the water-soluble cap. This modification allows drugs to get past the stomach and into the colon — a good direct-deposit way of delivering treatment for inflammatory bowel disease.[109]
- Dispersing a drug into Gelucire, with the addition of a small amount of a polymer called Sumikagel®, has been described. Gelucire plays the role of an erodible polymer matrix with a low rate of erosion. Sumikagel swells to various extents, depending on pH. This new dosage form disintegrates completely in an aqueous solution of pH 8 in less than 1 hour, while the rate of drug delivery remains constant.

Delivery of drug occurs by transient diffusion when the pH is between 1 and 2.[110]

- The transmucosal absorption of various peptides, such as insulin, calcitonin, tetragastrin, and thyrotropin-releasing hormone (TRH), could be improved by using additives, such as absorption enhancers and protease inhibitors.[125]
- Lectins have been used as specific bioadhesives, with many suitable properties for targeting of cells in the GI tract.[126]
- Oral absorption of parathyroid hormone in rats and monkeys as models of osteoporosis was facilitated by N-8(2hydroxy-4-methoxy)benzoylaminocaprylic acid as a novel delivery agent.[127]
- The introduction of biotin moiety in certain nonapeptides can alter its intestinal transport pathway, resulting in a significant improvement in the absorptive permeability by enhancing nonspecific passive and carrier-mediated uptake by means of a sodium-dependent multivitamin transporter.[128]
- A possible method to enhance oral absorption is to exploit the phenomenon of lipophilic modification and mono- and oligosaccharide conjugation. The delivery system can be conjugated to the drug in such a way as to release the active compound after it has been absorbed (i.e., the drug is converted to a pro-drug), or to form a biologically stable and active molecule (i.e., the conjugate becomes a new drug moiety). The use of lipid, sugar, and lipid–sugar conjugates has resulted in enhanced drug delivery.[129]
- "Lipid" formulations for oral administration of drugs generally consist of a drug involved in a blend of two or more excipients, which may be triglyceride oils, partial glycerides, surfactants, or co-surfactants. The primary mechanism of action that leads to improved bioavailability is usually avoidance or partial avoidance of the slow dissolution process, which limits the bioavailability of hydrophobic drug from solid dosage forms. Ideally, the formulation allows the drug to remain in a dissolved state throughout its transit through the GI tract. The availability of the drug for absorption can be enhanced by presentation of the drug as a solubilizate within a colloidal dispersion. This objective can be achieved by formulation of the drug in a self-emulsifying or self-microemulsifying system or, alternatively, by taking advantage of the natural process of triglyceride digestion. In practice, "lipid" formulations range from pure oils, at one extreme, to blends that contain a substantial proportion of hydrophilic surfactants or cosolvents, at the other extreme.[130]
- As a new oral drug delivery system for colon targeting, enteric-coated, timed-release, press-coated tablets (ETP tablets) have been developed by coating enteric polymer on timed-release, press-coated tablets composed of an outer shell of hydroxypropylcellulose and a core tablet containing diltiazem hydrochloride as a model drug. The re-

sults indicated that the tablets showed both acid resistance and timed release and they reached the colon after gastric emptying.[131]

- pH-sensitive interpolymer interactions between high molecular weight polyoxyethylene and poly(methacrylic acid co-methyl methacrylate) (EudragitEUD L100 of S100) were demonstrated and exploited to prepare coevaporates, or physical mixtures, of compressed matrix tablets containing prednisolone in order to deliver them to sites in the GI tract. Matrices based on plain EUD were found to exhibit a comparatively low release rate, more suited to an extended delivery to the colon than to a specific delivery to the ileum.[132]
- In order to develop an enzymatically controlled, pulsatile drug-release system based on an impermeable capsule body that contains the drug, an erodible pectin/pectinase plug was prepared by direct compression of pectin and pectinase in different ratios. It was found that drug release was controlled by the enzymatic degradation and dissolution of pectin.[133]
- The ability of glycostenoid (TC002) was investigated to increase the oral bioavailability of gentamicin. TC002 was found to be significantly more efficacious than sodium taurocholate, but similar in cutotoxicity. TC002 remained primarily in the GI tract following oral or intestinal administration and cleared rapidly from the body. It was only partly metabolized in the GI tract, but was rapidly and completely converted to its metabolite in plasma and urine.[134]
- Lectin-mediated mucosal delivery of drugs and vaccines, mucoadhesive DL-lactide/glycolide copolymer nanospheres coated with chitosan to improve oral delivery of elactonin, microspheres containing dexamethasone, synthetic peptides encapsulated in PLG microparticles, nanoparticles linked to vitamin B-12, and chitosan-cellulose multicore microparticles for controlled drug delivery were prepared.
- Cardinal Health, Inc. has developed controlled-release, oral, sustained-action technology (OSAT). This is a multiparticulate, HPMC-based, coating bead system that allows the active drug to diffuse out of pores in the bead. This system utilizes multiple beads that eliminate the concerns of dose dumping and has taste-masking properties.

VIII. Current development of oral drug delivery systems[74]

Developer	Product under Development
Cortecs & Rhone-Poulenc Rorer	Calcitonin and the diuretic peptide DDAVP
Cortecs	Insulin using macromol delivery system, Indomethacin formulation
Ethical Pharmaceuticals	Amiophylline formulation, Rhotard Delivery System, morphine and verapamil formulations

Developer	Product under Development
Gacell Laboratories and Pan	Multipore drug delivery system using diltiazem
Medica	Metoclopramide formulation
Hafslund, Nycomed	Furosemide in multiple unit, controlled-release capsule, Naproxen enteric-coated, Indomethacin and morphine using Repro-dose control-release system
Siegfried	Nifedipine capsule formulation
SmithKline Beecham	Mesalazine formulation
Erbamont, Proctor & Gamble	Mesalazine formulation
Lab Phoenix	Ranitidine sustained-release system
Taiyo Pharmaceutical	Sodium picosulfate
Kabi Pharm	Silfasalazine enteric-coated
Vuman	For treatment of hyperglycemia
Pharma Logic	Dantrolene, microCRYSTAL formulation for malignant hyperthermia
Biovail	Verapamil once-daily formulation
Orion	Verapamil formulation
Forest Laboratories	Cognine Synapton, physostigmine Synchron delivery system
Forest Labs, Sandoz	Thioridazine (Synchron)
Pharmed:Ferring	Vasopressin, Insulin
Pharmaceutical Development Associates	Insulin
R.P. Sherer:Johnson& Johnson	Loperamide, Polysol Sheresol system
Glenfair Pharmaceuticals	Magnesium chloride enteric-coated
Pharmos: Yissum	Submicron emulsion (SME) delivery system, lipophilic drugs in uniform minute droplets, physostigmine
TheraTech	STDC for site-specific targeted delivery in the colon
Recordati	Control-release suspension system (CRSS)
Faulding Glaxo Dainippon	Morphine sustained-release system Theophylline formulation
Nikken Chemical	Valproate sodium once-daily granule formulation
Elf Sanofi:Kyowa Hakko	Valproate sodium
Gebro Broschek	Theophylline long-acting
Pierre Fabre	Theophylline slow-release
Schering-Plough:Recordati	Theophylline once-daily
Verex	Indomethacin SR Formulation
Verex:Biovail	Naproxen Formulation OLipHEX (Osmotic lipid hydrogel complex) system, Zidovudin once daily for AIDS
Hisamatsu:Nissan Chemical Solvay	Ketoprofen formulation
Pharmatec International	Ketoprofen SURECAPS capsule delivery system
Alfa Schiapparelli	Naproxen formulation

Developer	Product under Development
Wassermann Monsanto Research Triangle Pharmaceuticals	Carbamazepine, microCRYSTAL
CytRX	Emulsion technology
Fisons	Pennkinetic delivery system dextromethorpham
Sparta	Spartaject,microcrystal/micro-droplet delivery system for Busulfan doxorubicin and aphidicolin
KV Pharmaceutical	Caltrate D, FerroSequels, nutritionals Liquette, solid drug delivery system for antacids. Meter-release containing beads or granules with the active drug coated with a rate-controlling system, e.g., antihistamines, nitroglycerine, theophylline, Vitamin C long-acting capsule
KV Pharmaceutical, Taisho Warner-Lambert	KV/24 drug delivery system
Alza	MOSTS (mucosal oral therapeutic system) Chronset Controlled-release Osmotic dosage formulation system
Alza:Monsanto	Verapamil, OROS
Alza:Pfizer	Glipizide, OROS
Alza:Pfizer:Bayer	Adalat, OROS; Procardia, OROS
Alza:Ciba-Geigy	Lopressor, OROS
Alza:Pfizer	Alpress. Prazosin, GITS, Minipress, OROS
Eurand	Isosorbide 5′-mononitrate using Diffutab control-release system Theophylline-Liquitard, Prazosin Diffutab, Diclofenac, Diffucaps, Ibuprofen, Diffutab system, Minitabs, multiparticulate dosing formulation Liquitard, drugs are microencapsulated by MICROCAP system and then are in the suspension form, MICROCAP for taste masking
Eurand:E.Merck	Pancreatin, lipase capsules
Elan	Sulindac-capsule, SODAS (Solid Oral Drug Absorption System), Cough-cold product, EL-715 for osteoporosis Verapamil, Trimethoprim/sulfamethoxazole using PharmaZome
Elan	INDAS (Insoluble Drug Absorption System) for dihydropyridine compounds, e.g., nifedipine, isradipine, nicardipine Formulations for propranolol, indomethacin, prazozin, Capsules, Carbamazepine taste masking.
Elan:Syntex:Roche	Naproxen formulation
Elan:Pasteur Merieux	Trimethoprim/silfamethoxazole using PharmaZome technology
Elan:Roussel-Uclaf	Theophylline using PharmaZome system

Extensive studies with inhaled insulin, nasal insulin, and oral insulin have produced interesting findings with pulmonary delivery for coverage, with short-acting insulin having the brightest prospects. Encapsulated islets

and biohybrid systems that place liver islets into an implanted device are in stages of development. Closing the loop with a continuous glucose sensor will be the only way to achieve truly normal blood glucose homeostasis by directing insulin delivery automatically on demand. Alternately, insulin has been delivered by a variety of routes (e.g., transdermal, buccal, ocular, rectal, vaginal, uterine, and subcutaneous).[135,143]

Successful oral delivery of insulin involves overcoming the barriers of enzymatic degradation, achieving epithelial permeability, and taking steps to conserve bioactivity during formulation processing. The use of enzyme (protease) inhibitors, permeation enhancers, calcium chelators, and polymer systems (with absorption modifiers) has been attempted to overcome these barriers. A synergistic approach, however, works best. The development of dosage forms with dual controlled-release characteristics using chicken or duck ovomucoids were investigated for enzymatic stability, permeability, and dissolution stability experiments. Biodegradable and nondegradable microspheres or nanospheres were studied for oral insulin delivery.[139,140–142,144,145]

Ovasome technology (Endorex Corp., Chicago, IL) is developing encapsulation of insulin/protein in liposomes, while Enisphere technology (New York) works with non-acylated alpha-amino acids as carriers for oral delivery of macromolecules and insulin. The M2 system (Nobex Corp., Research Triangle Park, NC) is based on the attachment of low molecular weight polymers to specific sites in the protein. These polymer conjugates have been reported to improve stability and absorption when compared with the performance of native protein.

In oral drug delivery, R.P. Scherer, Jenssen Pharmaceutica, and Pharmalyoc use lyophilization process and Zydis, Quicksolv, and Lyoc technologies, respectively,[149] while Cima Labs, Yamanouchi Pharma, Elan, Ethypharm, and Eurand use the tabletting process and Orasolv/Durasolv, WOWTABS, FEDAS, Flashtab, and Ziplets technologies, respectively. Biovail (Fuisz) uses the cotton-candy process and the Flashdose technology. Alza initially worked on the "Ringcap" technology, which was acquired by Alkermes. This system is based on a tablet preferentially film-coated, which is subsequently partially coated with a series of "rings" using an adaptation of the capsule-banding process. In this technology, the number of "rings" applied, and their respective thicknesses, provide the primary means for moderating the rate at which the drug is released from the final dosage form. In the matrix technology, two approaches were used in Contramid (Lactopharm) and Geomatrix (Skyepharma). Further developments include introduction of Smartrix and GlaxoSmithKline's Procise system. Combining conventional HPMC matrix technology with an upper and lower layer comprised mainly of the matrix polymer, this device purports to moderate drug release by matching an increase in surface area with the concomitant reduction in drug concentration within the device. The core matrix, in combination with an upper and lower compressed coating layer that erodes at a specific rate, is intended to provide a greater degree of precision over the manner in which the drug is released.

In the processing technologies,[146,147] BASF Pharma (now Abbott), Therics Sarnoff, Delsys, and Phoqus have developed new processes. In the Theriform (Therics) process, the technique uses an adaption of inkjet printing to fabricate tablets with precise architectures capable of providing a broad range of drug delivery possibilities. Delsys uses the Accudep process to apply electrostatically charged particles of a drug to a polymeric substratum held by an electrostatic module. Subsequently, the drug-loaded substratum is laminated with a second layer of polymeric film, and discs containing the drug are punched out from the laminate to create the final dosage form.[150–152] The technology employed by Phoqus represents an adaption of the electrophotography process employed in all common photocopying machines. Electrostatically applied coatings can be used to create unique appearance attributes, and an inherent ability to apply different coating formulations to different parts of the same tablet, or only to partially coat a tablet surface, provide a broad space in facilitating the design of highly specialized drug delivery systems (see Figure 5.4).[148]

Reo and Fredrickson[153] have discussed the latest developments in taste-masking science. Agents like sodium chloride, phosphatidic acid, and peppermint flavor are known to inhibit bitterness of select active pharmaceutical ingredients (API) molecules via a mechanism that takes place at the bitterness receptor in the taste buds. API crystallization techniques, such as crystal size distribution (CSD), spherical crystal agglomeration (SCA), and quasi-emulsion solvent diffusion (QESD), developed by solid-state scientists, chemical processing engineers, and formulation chemists can save time and resources for producing suitable API particles for taste and masking processing.[154–156]

Parenteral low molecular weight heparin (LMWH) has replaced warfarin as the standard of care for the prevention of deep-vein thrombosis and pulmonary embolism in high-risk hospitalized patients undergoing joint replacement or abdominal surgery. Compared with warfarin, LMWH has a significantly lower incidence of drug–drug interaction. The major disadvantage of LMWH therapy has been that it must be parenterally administered because it is ineffective when given orally. Several recent attempts to develop effective oral LMWH formulations have been reviewed by Sastry et al.[152] For example, complexes with tertiary amines, lipid-matrix-containing phosphatidylcholine from soy protein and medium-chain monoacyl glycerol and the use of glycerol esters of fatty acids and non-ionic surfactants. These authors also report the use of 8-[N2-hydroxybenzoyl)amino] caprylate (SNAC) and sodium 10-[N-(2-hydroxybenzoyl)amino]decanoate (SNAD) as delivery agents. They found that SNAC and SNAD facilitate the transport of LMWH across Caco-2-epithelial cells without opening the tight junctions or adversely affecting the structural integrity of the cell monolayer. Their studies also demonstrate that SNAC and SNAD facilitate oral LMWH absorption in rats and monkeys, and their combinations are not cytotoxic in a Caco-2 cell culture model.[136–138]

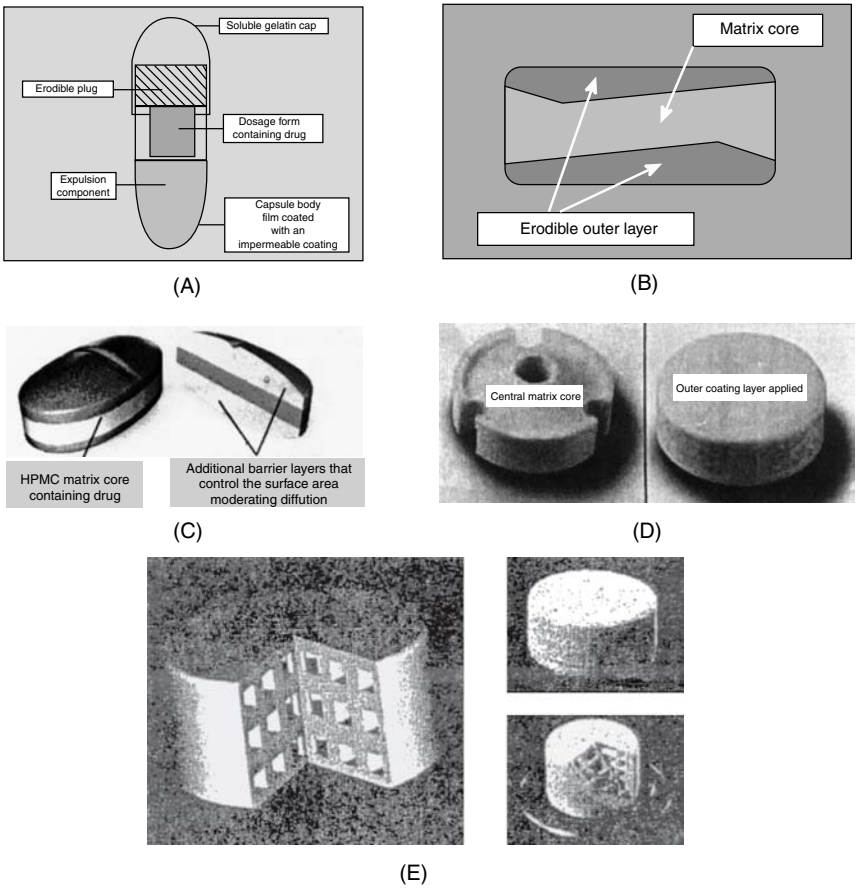

Figure 5.4 (A) Example of temporal delivery capsule technology. (B) Example of Smartrix technology. (C) Example of Geomatrix tablet. (D) Example of Procise technology. (E) Example of Therisys technology. (With permission, Russell Publ., *Am. Pharm. Rev.*, 4, 3, 28, 2001.)

In other experiments, it was reported that polymeric nanoparticles (NPs) prepared with biodegradable poly-epsilon-caprolactone and poly(lactic-co-glycolic)acid and nonbiodegradable positively charged polymers (Eudragit RS & RL), used alone or in combination, were evaluated *in vitro* and *in vivo* after a single oral administration of heparin-loaded NPs in rabbits. The authors concluded that the significant increases in anti-factor Xa activity and (aPTT)activated partial thromboplastin time confirmed the oral absorption in rabbits of heparin released from polymeric NPs.[157–160]

IX. Conclusion

The potential value of therapeutic drug delivery systems lies in a continuous controlled-release process that can proceed unattended for relatively long

periods. Ideally, these systems will eliminate the need for frequent dosing and control fluctuating blood levels.

Oral sustained-release dosage forms are, to a large extent, elementary in their design and often imprecise in their ability to release a drug at a constant rate. However, because GI transit time limits these drug delivery systems to 8 to 12 hours, and because of our lack of knowledge of fundamental processes in the GI tract at the molecular and cellular levels, design must be either self-contained systems (i.e., independent of the environment) or systems that are elementary. Presumably, the next generation of controlled-release oral dosage forms will be based in part on a strategy developed from a mechanistic understanding of GI physiology.[111]

Traditionally, an important element of oral controlled-release dosage forms has been the need for strict adherence to zero-order kinetics. Given that many drugs enjoy a reasonably wide therapeutic range and that 10 to 30% differences in blood-drug levels will usually not show a change in biological response, perhaps too much has been made of this requirement. Within experimental error, a number of release-rate kinetic orders cannot be distinguished on the basis of the resulting blood levels.[112–118]

It is apparent that controlled drug delivery is a strategy that will remain popular for the foreseeable future and that the oral route will be a dominant approach. To date, the majority of new products claiming to be controlled-release systems are really extensions of old technologies with no great improvement in clinical performance. Nonetheless, given the current efforts being made in oral controlled delivery and our increasing knowledge base in GI physiology, it is likely that a substantial number of new products will emerge in this decade.[119–124]

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