he number of products based on new drug delivery systems has significantly increased in the past few years, and this growth is expected to continue in the near future. Recent advances in the field of genomics have accelerated research of biopharmaceuticals, and today a large number of companies are busy developing protein- and peptide-based drugs. These biopharmaceuticals present challenges to drug delivery scientists because of their unique nature and difficulty in delivery through conventional routes. Therefore, future research will focus on the delivery of these complex molecules through different routes, including oral, nasal, pulmonary, vaginal, rectal, etc. This review is an update on some of the existing drug delivery technologies for oral controlled-release, delivery of large molecules, liposomes, taste masking, fast-dispersing dosage forms, and technology for insoluble drugs. Nasal, pulmonary, vaginal, and rectal routes also are briefly reviewed.

Evolution of an existing drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety, and efficacy. These days, drug delivery companies are engaged in the development of multiple platform technologies to get competitive advantage, extend patent life, and increase market share of their products.

In the 21st century, the pharmaceutical industry is caught between the downward pressure on prices and the increasing cost of successful drug discovery and development. The average cost and time for the development of a new chemical entity are much higher (approximately $500 million and 10–12 years) than those required to develop a novel drug delivery system (NDDS) ($20–50 million and 3–4 years). In the form of an NDDS, an existing drug molecule can get a new life, thereby increasing its market value and competitiveness and extending patent life. Limited formulations, patent expiry with subsequent entry of generic competition, and vertical integration have the entire pharmaceutical industry (approximately 350 drug delivery companies and 1000 medical device companies) focused on designing and developing new and better methods of drug delivery. There has been a significant increase in approvals of NDDSs in the past couple of years, and this is expected to continue at an impressive rate in the near future. The sale of drug delivery products is valued at more than $22 billion worldwide, and this growth is expected to continue into the present century. It is estimated that the drug delivery market will be at $120 billion by 2007.

At present, there are so many existing drug delivery technologies that a total compilation is not within the scope of this article. Yet an attempt is being made to compile some of the most successfully marketed drug delivery technologies. Most of the information is derived from the Internet sites of the major drug delivery companies.

Current status of drug delivery technologies
Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety, and improved patient compliance. The need for delivering drugs to patients efficiently and with fewer side effects has prompted pharmaceutical companies to engage in the development of new drug delivery systems. Today, drug delivery companies are engaged in the development of multiple platform technologies for controlled release, delivery of large molecules, liposomes, taste-masking, oral fast-dispersing dosage forms, technology for insoluble drugs, and delivery of drugs through intranasal, pulmonary, transdermal, vaginal, colon, and transmucosal routes.
Oral controlled release

Oral ingestion is the traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of the drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which, in most situations, often results in constantly changing, unpredictable, and often sub- or supra-therapeutic plasma concentrations leading to marked side effects. An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled-release (CR) delivery systems provide a uniform concentration/amount of the drug at the absorption site and thus, after absorption, allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. CR products are formulations that release active drug compounds into the body gradually and predictably over a 12- to 24-hour period and that can be taken once or twice a day. Typically, these products provide numerous benefits compared with immediate-release drugs, including greater effectiveness in the treatment of chronic conditions, reduced side effects, greater convenience, and higher levels of patient compliance due to a simplified dosing schedule. Because of the above advantages, such systems form the major segment of the drug delivery market.

A number of techniques are used to achieve controlled release of drugs via the oral cavity. Some of these techniques are reviewed briefly as follows.

Osmotic systems utilize osmotic pressure as the driving force for the delivery of drugs. In its simplest design, it consists of an osmotic core (a drug with or without an osmagent), which is coated with a semipermeable membrane, and a delivery orifice is created with a mechanical or laser drill. When the dosage form comes in contact with water, water is imbibed because of the resultant osmotic pressure of the core and the drug is released from the orifice at a controlled rate. This system, known as elementary osmotic pump (EOP), was first developed by Felix Theeuwes of Alza Corporation (USA). A number of modifications of this system are available today, like the push-pull osmotic pump, which is a bilayer tablet and is suitable for the delivery of highly or poorly water-soluble drugs. The upper layer consists of a drug along with osmotic agents. The lower layer consists of polymeric osmotic agents. The tablet is coated with a semipermeable membrane, and a delivery orifice is created similar to that of an EOP. Figure 1 shows the schematic diagram of these two types of systems. Alza Corporation is a leader in the field of oral osmotic systems, and some of the commercially marketed products based on this technology are listed in Table I.

MacroCap (Biovail Corporation International, Canada) utilizes a controlled-release pellet system, which is based on the coating of pellets containing pharmaceutical compounds with specialized polymers and plasticizers to control the rate and location of drug release in the gastrointestinal (GI) tract. The MacroCap system uses the features of pH-activated or pH-independent diffusion, osmotic diffusion, or a combination of these mechanisms. The pH-activated diffusion system uses specifically designed coating polymers to control the delivery of drugs depending on the pH environment of the GI tract. Under the osmotic diffusion system, the rate of release of the drug from the pellets is controlled by a combination of principles involved in osmosis and diffusion.

Micropump Oral Controlled Delivery System (Flamel Technologies, France) is suitable for drugs that require an extended absorption time in the small intestine. Each Micropump dosage form is composed of thousands of microparticles ranging in size between 200 and 400 μm and having a bioadhesive surface. Each microparticle contains a drug crystal or a drug solution or granule enclosed in a polymer coating that acts as a shell through which the drug can be released under the effect of osmotic pressure. Modulating the thickness and composition of the polymer coating can control the rate and duration of drug delivery.

MODAS or Multiporous Oral Drug Absorption System (Elan Corporation, Ireland) is surrounded by a non-disintegrating, timed-release coating, which after coming in contact with gastrointestinal fluid is transformed into a semipermeable membrane through which the drug diffuses in a rate-limiting manner. The tablet consists of a core of active drug plus excipients. This is then coated with a solution of insoluble polymers and soluble excipients. After ingestion, the fluid of the gastrointestinal tract dissolves the soluble excipients in the outer coating leaving just the insoluble polymer, thereby forming a network of tiny, narrow channels connecting fluid from the GI tract to the inner drug core of water-soluble drug. This fluid passes through these channels into the core, dissolves the drug, and a resultant solution of drug diffuses out in a controlled manner to the outside. The addition of excipients, such as buffers can help produce a microenvironment within the
tablet that facilitates more predictable release rates and absorption. Examples of MODAS products developed by Elan include Bron-12 (a 12-hour multicomponent over-the-counter [OTC] cough and cold product) and once-daily potassium chloride. **SCOT** or Single Composition Osmotic Tablet System (Andrx Pharmaceuticals, USA) is also based on osmotic principles and utilizes various osmotic modulating agents as well as polymer coatings to provide a zero-order release of a drug. **Porta** System (Andrx Pharmaceuticals) utilizes an osmotic core, typically containing a water-soluble drug. The core includes a water-soluble component and a continuous polymer coating. The purpose of the soluble agent is to expand the core and thereby create microporous channels through which the drug is released. **Zer-Os** tablet technology (ADD Drug Delivery Technologies AG, Switzerland) is an osmotic system developed specifically for the delivery of lipophilic compounds. The tablet consists mainly of a core of poorly water-soluble drug along with gel-forming agents and standard excipients. The gel-forming agent, after coming in contact with water, forms a gel of an appropriate viscosity, and a suspension of a poorly water-soluble agent is formed and is pushed out of the orifice at a controlled rate. **Tegetrol XR**, a successful product on the US market, is based on this technology as well.

In addition to osmotic principles, numerous other approaches also exist for the delivery of drugs in a controlled manner, some of which are briefly reviewed in the following sections.

**Ceform microsphere technology** (Fuisz Technology Ltd., USA) allows the production of uniformly sized and shaped microspheres of pharmaceutical compounds. These microspheres are almost perfectly spherical, having a diameter that is typically 150 to 180 μm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres can be formulated for enhanced absorption (Ceform EA) or taste isolation (Ceform TI) and may be coated for controlled release (Ceform CR), provided with an enteric coating (Ceform EC), or combined into a fast/slow release combination (Ceform EA/CR).

**CONSURF** or Constant Surface Area Drug Delivery Shuttle (Biovail Corporation International) releases drug by the concurrent swelling and dissolution of a matrix tablet. A constant surface area is presented during the drug’s transit through the GI tract.

**Contramid** (Labopharm Inc., Canada) utilizes excipients (mainly starch) for the controlled delivery of drugs. The chemical cross-linking of a starch consisting mainly of amylase leads to Contramid. During the cross-linking, bridges are formed between the polysaccharides. Varying the quantity of cross-linking reagent used in the manufacturing process can control the degree of the cross-linking. Once the Contramid dosage form is in the stomach, gastric fluids turn Contramid’s surface to gel and the resulting semi-permeable membrane stabilizes rapidly. This membrane, which does not begin to

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**Table 1: Some commercially marketed oral osmotic systems.**

<table>
<thead>
<tr>
<th>Product name</th>
<th>Chemical</th>
<th>developer/marketer</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acutrim</strong></td>
<td>Phenylpropanolamine</td>
<td>Alza/Heritage</td>
<td>Appetite suppressant</td>
</tr>
<tr>
<td><strong>Alpress LP</strong></td>
<td>Prazosin</td>
<td>Alsa/Pfizer (France)</td>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>Calan SR</strong></td>
<td>Verapamil</td>
<td>Alza/G.D. searle</td>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>Cardura XL</strong></td>
<td>Doxazosin mesylate</td>
<td>Alza/Pfizer (Germany)</td>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>Concerta</strong></td>
<td>Methylphenidate</td>
<td>Alza</td>
<td>Attention Deficit</td>
</tr>
<tr>
<td><strong>Covera HS</strong></td>
<td>Verapamil</td>
<td>Alza/G.D. searle</td>
<td>Hyperactivity Disorder</td>
</tr>
<tr>
<td><strong>Ditropan</strong></td>
<td>Oxybutynin Chloride</td>
<td>Alza/UCB Pharma</td>
<td>Overactive bladder</td>
</tr>
<tr>
<td><strong>DynaCirc CR</strong></td>
<td>Isradipine</td>
<td>Alza/Novartis</td>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>Efidac/24</strong></td>
<td>Pseudoephedrine</td>
<td>Alza/Novartis</td>
<td>Cold medication</td>
</tr>
<tr>
<td><strong>Efidac 24 Chlorpheniramine</strong></td>
<td>Chlorpheniramine</td>
<td>Alza/Novartis</td>
<td>Anti-allergic</td>
</tr>
<tr>
<td><strong>Efidac 24 Pseudoephedrine/Brompheniramine</strong></td>
<td>Pseudoephedrine and Brompheniramine</td>
<td>Alza/Novartis</td>
<td>Anti-allergic and cold treatment</td>
</tr>
<tr>
<td><strong>Glucotrol XL</strong></td>
<td>Glipizide</td>
<td>Alza/Pfizer</td>
<td>Anti-diabetic</td>
</tr>
<tr>
<td><strong>Minipress XL</strong></td>
<td>Prazosin</td>
<td>Alza/Pfizer</td>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>Procardia XL</strong></td>
<td>Nifedipine</td>
<td>Alza/Pfizer</td>
<td>Hypertension/angina</td>
</tr>
<tr>
<td><strong>Sudafed 24 hour</strong></td>
<td>Pseudoephedrine</td>
<td>Alza/Warner Lambert</td>
<td>Nasal decongestant</td>
</tr>
<tr>
<td><strong>Teczem</strong></td>
<td>Enalapril and Diltiazem</td>
<td>Merck/Aventis</td>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>Tiamate</strong></td>
<td>Diltiazem</td>
<td>Merck/Aventis</td>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>Volmax</strong></td>
<td>Albuterol</td>
<td>Alza/Muro Pharmaceuticals</td>
<td>Bronchospasm</td>
</tr>
</tbody>
</table>
break down until it reaches the colon, ensures that there is a regular release of the active ingredients contained in the dosage form.

**Dimatrix** or Diffusion Controlled Matrix System (Biovail Corporation International) consists of either beads made by extrusion–spherization or by powder/solution layering on nonpareil beads or in the form of a tablet matrix. The mechanism of release is by diffusion of dissolved drug molecules. **Multipart** or Multiparticle Drug Dispersing Shuttle (Biovail Corporation International) consists of a tablet that carries controlled-release beads or pellets through the GI tract while maintaining their integrity and release properties. Release and distribution of the beads is triggered by superdisintegration of the tablet.

**DPHS** or Delayed Pulsatile Hydrogel System (Andrx Pharmaceuticals) is designed for use with hydrogel matrix products that are characterized by an initial zero-order release of drug followed by rapid release. This release profile is achieved by the blending of selected hydrogel polymers to achieve a delayed pulse.

**DUREDAS** or Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer-tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct-compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner. A further extension of the Duredas technology is the production of controlled-release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each is controlled to maximize therapeutic effect of the combination. Again both immediate-release and controlled-release combinations of the two drugs are feasible.

**Gastric retention system** (DepoMed Inc., USA) consists of a drug containing polymeric units that, if taken with a meal, remain in the stomach for an extended period of time to provide continuous, controlled delivery of an incorporated drug.

**Geomatrix** (Skye Pharma Plc., USA) is a platform of oral controlled-release technology that controls the amount, timing, and location of the release of drug compounds into the body. Geomatrix system is a multilayer tablet with a matrix core containing the active ingredient and one or more modulating layers (barriers) applied to the core during the tableting process. The function of these barriers is to delay the interaction of the core with the dissolution medium. Eight Geomatrix technologies are designed to meet a wide range of therapeutic objectives: Zero-order release provides a constant rate of drug release over a defined period of time; binary release is used to provide the controlled release of two different drugs in a single tablet; quick–slow release provides a quick burst of drug release followed by a constant rate of release over a defined period of time; slow–quick release provides an initial constant rate of release followed by a quick burst of drug release at a predetermined time; positioned release delivers the drug to a predetermined position in the digestive system before it begins to release the active drug compounds; accelerated release provides a constantly accelerating rate of drug release; delayed release provides a predetermined time lag before it begins releasing drug molecules; multiple pulse provides an initial quick burst of drug release followed by a predetermined period of no release. Some of the drugs that are marketed based on this technology are diltiazem hydrochloride, nifedipine, and diclofenac sodium.

**GMHS** or Granulated Modulating Hydrogel System (Andrx Pharmaceuticals) incorporates hydrogel and binding polymers with the drug, which is formed into granules and then pressed into tablet form.

**IPDAS** or Intestinal Protective Drug Absorption System (Elan Corporation) is a multiparticulate tablet technology, that has been developed to enhance the gastrointestinal tolerability of potentially irritant or ulcerogenic drugs. Unlike other tablet formulations, IPDAS is composed of numerous high-density controlled-release beads. Each bead is manufactured by a two-step process that involves the initial production of a micromatrix of drug embedded in polymer and the subsequent coating of this micromatrix with time-release coatings that are transformed into a rate-limiting semipermeable membrane in vivo. After ingestion, the tablet rapidly disintegrates and beads are dispersed into the stomach and subsequently pass into the duodenum and along the GI tract in a controlled and gradual manner, independent of the feeding state. Drug release from each bead occurs by a diffusion process through the micromatrix and subsequently through the pores in the rate-controlling semipermeable membrane. An immediate-release granulate also can be included in the tablet and may be required for a fast onset of action. IPDAS products are approved worldwide, and Elan’s Naprelan product (once-daily naproxen sodium) is sold in the US market.

**Multipor** technology (Ethical Holdings Plc., UK) consists of a tablet core of an active drug, which is surrounded by a water-insoluble polymer membrane. The membrane consists of minute water-soluble particles that, after coming in contact with water, dissolve and form pores from which the drug is released. This technology also can be applied to pellets, granules, or minitablets. One or more drug substances also can be incorporated into the membrane, which can provide an immediate-release layer.

**Pharmazome** or Microparticulate Drug Delivery Technology (Elan Corporation) consists of combinations of polymers and drugs in the size range of 5 to 125 μm. Each microparticle is a micromatrix of drug embedded uniformly throughout an insoluble polymer and is produced by either a spray drying or emulsion technique. By varying the amount and nature of the polymer used to form the micro
Particle, this technology allows controlled-and/or delayed-release of drug from the formulation. In addition, this technology also can be used for taste masking because it acts as a means of physically preventing a drug from going into solution in the mouth and coming into direct contact with taste receptors. For the purpose of palatability, 125 μm is set as the upper limit for Pharmazomes because these particles have a gritty feeling that may be unacceptable to consumers. Pharmazomes can be subsequently incorporated into a variety of delivery systems like chewable tablets, effervescent tablets, oral ready-made aqueous and non-aqueous suspensions, reconstitutable powders, and unit-dose sachet or sprinkle systems. Products using Pharmazeume technology are currently approved in Japan, Europe, and Central and South America and include twice-daily theophylline.

PPDS or Pelletized Pulsatile Delivery System (Andrx Pharmaceuticals) is designed for use with products that require a pulsed release of the drug. This technology uses pellets that are coated with specific polymers and agents to control the release rate of the microencapsulated drug. By varying the proportion and composition of the polymer mixtures, formulations can practically control the release rate of the drug. Peltab System (Andrx Pharmaceuticals) utilizes polymer-coated drug pellets or drug crystals that are manufactured into tablets. In order to provide controlled release, a water-insoluble polymer is used to coat discrete drug pellets or crystals that then can resist the action of fluids in the GI tract. This technology incorporates a strong polymer coating enabling the coated pellets to be compressed into tablets without significant breakage.

PRODAS or Programmable Oral Drug Absorption System (Elan Corporation) is a multiparticulate drug delivery technology that is based on the encapsulation of controlled-release minitablets in the size range of 1.5 to 4 mm in diameter. This technology represents a combination of multiparticulate and hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in one dosage form. Minitablets with different release rates can be combined and incorporated into a single dosage form to provide the desired release rates. These combinations may include immediate-release, delayed-release, and/or controlled-release minitablets. In addition to controlled absorption over a specified period, PRODAS technology also enables targeted delivery of drug to specified sites of absorption throughout the GI tract. Combination products also are possible by using minitablets formulated with different active ingredients.

Reduced irritation system (Depomed, Inc.) is designed to significantly reduce local gastrointestinal irritation from the effects of certain drugs. This system consists of an outer gelatin capsule that is designed to rapidly disintegrate upon ingestion to deliver multiple small spherical pellets. The spherical pellets are composed of an inert matrix of polymeric material in which the active ingredient is homogeneously dispersed in its solid state.

RingCap (Alkermes Inc., USA) combines matrix tablets and existing capsule banding processes to create controlled-release solid oral dosage forms. The RingCap system utilizes bands of insoluble polymer on a matrix tablet. The manufacturing process involves compressing the drug into cylindrical matrix tablets that are subsequently film coated. Then, existing capsule-banding technology is used to apply two or more polymeric rings around the circumference of the matrix tablet. These bands lower the initial release of the drug by reducing the surface area exposed. As the matrix tablet erodes, new surface areas are created underneath and around the bands, thus increasing the rate of release. The release rate of the drug substance can be designed to remain nearly constant or even increase with time by adjusting the number and width of polymer bands.

SODAS or Spheroidal Oral Drug Absorption System (Elan Corporation) is a multiparticulate drug-delivery technology and consists of controlled-release beads that can be produced in the range from 1 to 2 mm in diameter. Each bead begins as an inert core onto which the drug is applied, followed by a number of layers of soluble and insoluble polymers combined with other excipients to produce the rate-controlling layer. Drug release from these beads occurs by a diffusion process. Within the GI tract, the soluble polymers dissolve, leaving pores within the outer membrane. Fluid then enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the in vivo dissolution and absorption phases. The immediate environment of the drug within the seed core can be manipulated by use of excipients to ensure optimal stability and solubility. These controlled-release beads can be packaged into a capsule or compressed into a tablet to produce the final dosage form. Products utilizing SODAS technology are approved and marketed throughout Europe, the US, and Japan and include once-daily diltiazem and once-daily verapamil. Cardizem SR and CD are twice- and once-daily formulations, respectively, of diltiazem hydrochloride (based on SODAS technology) developed by Elan in partnership with Hoechst Marion Roussel. Verelan was the first verapamil controlled-release formulation (based on SODAS technology) in which the extent or rate of absorption was not affected by food intake. In addition, the capsule could be opened and the beads sprinkled on soft food for those patients unable to swallow traditional dosage forms.

SMHS or Solubility Modulating Hydrogel System (Andrx Pharmaceuticals) is designed for products utilizing a hydrogel-based dosage system that provides sustained release without the need to use special coatings or structures, both of which add to the cost of manufacturing. This technology avoids the initial burst effect commonly observed with other sustained-release hydrogel formulations. Diltia XT, marketed by Andrx Pharmaceuticals, is based on this technology and is used for the treatment of hypertension and angina.

SPDS or Stabilized Pellet Delivery System (Andrx Pharmaceuticals) is designed specifically for unstable drugs and incorporates a pellet core of drug and protective polymer outer layer(s).

SQZGel oral controlled-release system (Macromed, Inc., USA) is an oral delivery system based on patented pH-sensitive hydrogels comprised of combinations of FDA-approved generally recognized as safe (GRAS) polymers. In response to internal or external pH levels, and by design, this system evenly releases a drug over an
8- to 20-hour period based on the delivery needs of the therapy. SQZGel is manufactured by an inexpensive standard tablet dosage form technique.

**TIMERx** (Penwest Pharmaceuticals Co., USA) is a controlled-release drug delivery technology applicable to a broad range of orally administered drugs. This technology is based on an agglomerated hydrophilic matrix. The matrix consists of two pharmaceutically acceptable polysaccharides, locust bean gum and xanthan gum. Interactions between these components in an aqueous environment form a tight gel with a slowly eroding core from which the drug is released at a controlled rate for an extended period of time. Slofedipine XL (nifedipine) and Cystrin CR (oxybutynin) are based on this technology and are marketed in Europe.

**KV** Pharmaceuticals (USA) has developed technologies for controlled delivery of drugs that includes KV/24, which is a multiparticulate technology that can combine several different drug compounds, each requiring its own unique release profile, in a single tablet form that can be taken orally once every 24 hours. **Meter Release** is a twice-a-day dosing, polymer-based drug delivery system that offers different release characteristics than KV/24 and is used for products that require a drug release rate of 8 to 12 hours. Symatrix is a microparticulate formulation that employs smaller particles than KV/24 and Meter Release. Symatrix encapsulates therapeutic agents that improve a drug’s absorption in the body when precise release profiles are less important. Spheroid combines equipment technology with formulation expertise. Each particle has its own matrix as the rate-controlling mechanism for the release of its contents. These particles can be filled into hard gelatin capsules or can be compressed into tablets. Orasert is designed as a solid oral dosage system that possesses bioadhesive and controlled-release properties. Orasite is a controlled-release muco-adhesive delivery system administered orally in solid or liquid form.

**Triglas** technology (Ethical Holdings Plc.) is mainly for water-insoluble drugs and is based upon formulating drug with appropriate additives to form a solid solution of drug that can be coated onto the carrier particles. These particles then can be made into tablets. **Rhotard** (Ethical Holdings Plc.) is based on double-matrix technology that involves two granulation stages during the manufacturing process.

**Large-molecule delivery**
Research efforts in the field of genomics are expected to accelerate the discovery of new therapeutic biomolecules, placing an increased demand on the development of delivery systems for these drugs. This class of drugs is usually characterized by large size, fragile nature, short biological half-life, and limited ability to cross cell membranes. These properties, along with the methods of administration of biopharmaceuticals, can limit their clinical applications to certain disease states that warrant the expense and inconvenience of frequent injection. At present, a large number of companies are working in this area, as evidenced by the increasing number of available technologies for delivering these compounds.

**BEODAS or Bioerodable Enhanced Oral Drug Absorption System** (Elan Corporation) is an oral microparticulate drug delivery technology designed for the delivery of macromolecules and is based on the entrapment of active pharmaceutical entities in a range of submicron sizes within biodegradable polymer matrices. Further modifications to the BEODAS platform technology have the potential for targeted delivery and enhanced absorption of pharmaceutical entities that normally are not amenable to oral administration.

**DepoFoam** (DepoTech Corporation, USA) drug delivery system consists of microscopic spherical particles composed of hundreds to thousands of nonconcentric chambers (depots) encapsulating the drug to be delivered. The individual chambers are separated by a bilayer lipid membrane made up of synthetic duplicates of lipids found naturally in the body, resulting in a material that is both biodegradable and biocompatible. The DepoFoam system provides either local site or systemic delivery and can be administered by a number of routes, including intrathecal, subcutaneous, intramuscular, and intra-articular. Typically, a DepoFoam particle consists of less than 10% lipid and 90% aqueous drug solution, giving it a high loading factor. DepoFoam formulations maintain a drug in its therapeutic window for periods ranging from days to many weeks, allowing lower initial drug levels and significantly fewer doses. DepoFoam technology is applicable across a variety of compounds, including small molecules, proteins, peptides, DNA, and vaccines. Some of the products like **DepoCyt** (cytarabine), **DepoMorphine** (morphine sulfate), and **DepoAmikacin** (amikacin) are based on this technology.

**DUROS** (Alza Corporation) is based on implant technology, which provides an alternative for the delivery of a wide range of therapeutic compounds, including peptides, proteins, and other bioactive macromolecules. These implants are miniature titanium cylinders designed to provide continuous osmotically driven delivery of drugs within the body for up to one year. Following implantation, DUROS implants enable continuous, precise delivery of the therapeutic compound at rates as low as 1% of a drop of water per day. The cylinder is manufactured from titanium because of the material’s tolerability to human tissue and its long use in medical devices such as implantable defibrillators and joint replacements. The cylinder protects therapeutic agents from degradation in the body and enables a drug to remain stable for extended periods of time. Recently, Viadur (leuprolide acetate implant), which is based upon this technology, has been approved for once-yearly palliative treatment of advanced prostate cancer.

**LODCAS or Localized Drug Absorption System** (Elan Corporation) is a novel targeted oral drug delivery technology. This technology utilizes targeting ligands, that specifically bind to certain absorption sites located on the apical surface of the epithelium cells of the human GI tract. These ligands are attached to coated microparticles of protein and peptide drugs that serve to protect their contents from the hostile environment of the GI tract. These are subsequently packaged in enteric-coated capsules that deposit the particles at appropriate sites of absorption within the GI tract.

**Macromol Systems** (Cortecs International Ltd., UK) enable polypeptides and proteins to be administered by the oral route rather than by injection. **Oral Mucosal Vaccines** (Cortecs International Ltd.) can be administered by mouth and act by presenting the antigen to specialized cells within the intestine that pick up small par-
articles via the Peyer’s Patch and can process them into the immune system to stimulate a defensive response at mucosal sites.

**Medipad** (Elan Corporation) is a patient-friendly system that enables controlled parenteral delivery while minimizing discomfort. This system is designed for the delivery of a broad range of compounds, from small molecules to proteins and peptides. Medipad is a low-cost, disposable, single-use system that combines unique microinfusion technology with an integral subcutaneous probe. An adhesive backing fixes the system discreetly against the user’s chest or abdomen where it continuously dispenses drug for up to 48 hours. It is the only technology that currently combines the simplicity of a patch with the delivery capabilities of an infusion pump. The Medipad technology can be tailored to a range of delivery volumes, delivery rates, and delivery profiles (bolus, extended bolus, continuous, or continuous plus bolus).

**Oral vaccines:** Elan Corporation and Endorex Corporation, a US biotechnology company, have formed a joint venture to develop a portfolio of technologies that will permit the oral administration of vaccines. The technology focuses on two different approaches for oral delivery of antigens through intestinal epithelial tissue. These are the production of micro- and nanoparticles of a defined size range containing antigens dispersed within a bioerodible polymer matrix and polymerized liposomal vesicles in which antigens are enclosed in a stable membrane. Both of these technologies protect antigens from the hostile environment of the GI tract and ensure that they are presented in an intact form to the mucosal surface for absorption.

**ProLease and Medisorb** (Alkermes Inc., USA) are two patented and proprietary processes for creating injectable sustained-release products lasting from days to months. ProLease is specifically designed for complex and fragile bioactive molecules such as proteins, and Medisorb is designed for traditional small molecules and peptides. Both technologies are microsphere-based delivery systems composed of the desired bioactive molecule incorporated into a matrix of poly-(DL-lactide-coglycolide), a common biodegradable medical polymer. Microspheres are packaged in vials as a dry free-flowing powder. Before administration the microspheres are suspended in an aqueous vehicle and administered by subcutaneous or intramuscular injection. Release profiles can be adjusted by manipulation of formulation parameters and by control of the fabrication process.

### Transdermal and topical delivery
Systemic delivery of drugs via transdermal routes has generated considerable interest during the last decade. Transdermal drug delivery systems (TDDS) deliver drugs through the skin into the systemic circulation at a predetermined rate.

#### Table II: Some of the commercially marketed transdermal systems.

<table>
<thead>
<tr>
<th>Product name</th>
<th>Chemical</th>
<th>Developer/Marketer</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alora</td>
<td>Estradiol</td>
<td>TheraTech/Proctor and Gamble</td>
<td>Postmenopausal syndrome</td>
</tr>
<tr>
<td>Androderm</td>
<td>Testosterone</td>
<td>TheraTech, Inc./GlaxoSmithKline</td>
<td>Hypogonadism in males</td>
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<tr>
<td>Catapres-TTS</td>
<td>Clonidine</td>
<td>Alza/Boehinger Ingelheim</td>
<td>Hypertension</td>
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<td>Climaderm</td>
<td>Estradiol</td>
<td>Ethical Holdings, Plc/Wyeth-Ayerest</td>
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<tr>
<td>Climara</td>
<td>Estradiol</td>
<td>3M Pharmaceuticals/Berlex Labs</td>
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<td>CombiPatch</td>
<td>Estradiol/Norethynadone</td>
<td>Noven Pharmaceuticals, Inc. Aventis</td>
<td>Hormone replacement therapy</td>
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<td>Deponit</td>
<td>Nitroglycerin</td>
<td>Schwarz-Pharma</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Duragesic</td>
<td>Fentanyl</td>
<td>Alza/Janssen Pharmaceuticals</td>
<td>Moderate/severe pain</td>
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<tr>
<td>Estraderm</td>
<td>Estradiol</td>
<td>Alza/Novartis</td>
<td>Postmenopausal syndrome</td>
</tr>
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<td>Fematrix</td>
<td>Estrogen</td>
<td>Ethical Holdings/Solvay Healthcare Ltd.</td>
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<td>FemPatch</td>
<td>Estradiol</td>
<td>Parke-Davis</td>
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<td>Habitrol</td>
<td>Nicotine</td>
<td>Novartis</td>
<td>Smoking cessation</td>
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<td>Mintran</td>
<td>Nitroglycerin</td>
<td>3M Pharmaceuticals</td>
<td>Angina pectoris</td>
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<tr>
<td>Nicoderm</td>
<td>Nicotine</td>
<td>Alza/GlaxoSmithKline</td>
<td>Smoking cessation</td>
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<td>Nicotrol</td>
<td>Nicotine</td>
<td>Cygnus Inc./McNeil Consumer Products, Ltd.</td>
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<td>Nitrodisc</td>
<td>Nitroglycerin</td>
<td>Roberts Pharmaceuticals</td>
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<td>Nitro-dur</td>
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<td>Key Pharmaceuticals</td>
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<td>Nuvelle TS</td>
<td>Estrogen/Progestosterone</td>
<td>Ethical Holdings, Plc./Schering</td>
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<td>Prostep</td>
<td>Nicotine</td>
<td>Elan Corp./Lederle Labs</td>
<td>Smoking cessation</td>
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<td>Testoderm TTS</td>
<td>Testosterone</td>
<td>Alza Corp.</td>
<td>Hypogonadism in males</td>
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<td>Transderm-Scop</td>
<td>Scopolamine</td>
<td>Alza/Novartis</td>
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<td>Transderm Nitro</td>
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<td>Vivelle</td>
<td>Estradiol</td>
<td>Noven Pharmaceuticals, Inc./Novartis</td>
<td>Postmenopausal syndrome</td>
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transdermal applications to the skin. Semisolid site-release configuration for administration of drugs through the skin.

Iontophoresis utilizes a high-voltage (>100 V) pulse for a very short duration (μs to ms) to create new aqueous pathways (pores) across lipid-containing barriers, forcing the drug molecule into systemic circulation. Iontophoresis is the application of ultrasound energy to enhance percutaneous drug absorption. Some of the successful technologies in this field are as follows:

**Dermaflex** (Elan Corporation) is a passive transdermal patch employing a hydrogel matrix in which a pharmaceutical compound is incorporated. Dermaflex regulates the availability and the absorption of pharmaceutical compounds in a manner that may allow controlled and efficient delivery.

**Dermasite** (KV Pharmaceuticals) is a semisolid site-release configuration for topical applications to the skin.

**D-trans** (Alza Corporation) is a transdermal system that provides rate-controlled administration of drugs through the skin.

These systems resemble small adhesive bandages and can offer multiday or weekly dosing and improved patient compliance.

**E-trans** (Alza Corporation) is an electrotransport system that uses low-power electric current to control drug administration through intact skin. E-trans systems are being developed to provide continuous drug delivery as well as patient-controlled pulsatile delivery.

**Microponge systems** (Advanced Polymer Systems Inc., USA) are based on microscopically sized microspheres that can bind, suspend, or entrap a wide variety of substances and incorporate them into a formulated product, such as gel, cream, liquid, or powder. Microspunge systems are used primarily as reservoirs for releasing active ingredients in an extended period of time and as receptacles for absorbing undesirable substances, such as excess skin oil. EveryStep (odor-fighting foot powder), Exact acne treatment (a cream formulation of benzoyl peroxide), and Retino-A-Micro (tretinoin gel) are based on this technology.

**Polytrap systems** (Advanced Polymer Systems Inc.) are designed to absorb skin oils and eliminate shine, provide a smooth and silky feel to product formulations, entrap and deliver various ingredients in personal care products, and convert liquids into powders.

**TheraDerm-LRS** (Theratech, Inc., USA) is a liquid reservoir system. Numerous drug formulations can be incorporated into a TheraDerm-LRS patch because the system is not rate limiting to the administration of the drug and the drug reservoir is isolated physically from the adhesive within the system.

**TheraDerm-MTX** (Theratech Inc.) is a matrix system based on an adhesive matrix patch design. The drug is incorporated into the adhesive, resulting in a light and flexible patch that conforms to the skin for maximum adhesion and comfort.

**TheraPatch** (LecTec Corporation, USA) is a self-adhering patch that delivers medications topically into the skin for localized pain relief and therapeutic treatment.

**Transdermal drug delivery systems** (Cygnus Inc., USA) provide the controlled release of drugs directly into the bloodstream through intact skin. By delivering a steady flow of drugs into the bloodstream for an extended period of time, transdermal systems can avoid the peak-and-effect of oral or injectable therapy and can enable more controlled effective treatment.

**Liposomal delivery**

Liposomes are microparticulate lipidoidal vesicles and have been used as a carrier for the improved delivery of a variety of drugs such as chemotherapeutic agents, imaging agents, antigens, genetic materials, immunomodulators, etc. Liposomes are a family of vesicular structures based on lipid bilayers surrounding aqueous compartments. In the majority of cases, lipid complexes and liposomal pharmaceuticals provide less toxicity and better efficacy than the active ingredient.

Conventional liposomes are typically composed of only phospholipids (neutral and/or negatively charged) and/or cholesterol. These are characterized by a relatively short blood circulation time. To overcome this problem, long-circulating liposomes (also called stealth or sterically stabilized liposomes) have been developed. These stealth liposomes carry a polymer coating to obtain prolonged circulation times. Targeted liposomes (immunoliposomes) may be either conventionally or sterically stabilized and have specific antibodies or antibody fragments on their surface to enhance target site binding. Cationic liposomes are still under development for improving the delivery of genetic material. A number of products based on liposomes have already been approved for marketing (see Table III), and more are awaiting approval. Companies such as ADD Drug Delivery Technologies AG (Switzerland), DepoTech Corporation (USA), Nexstar Pharmaceuticals (USA), Novavax Inc. (USA), The Liposome Com-

<table>
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<tr>
<th>Trade Name</th>
<th>Chemical</th>
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<td>AmBisome</td>
<td>Amphotericin B</td>
<td>NeXstar Pharmaceuticals</td>
<td>Systemic fungal infections</td>
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<td>Abelcet</td>
<td>Amphotericin B</td>
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<td>Amphotec</td>
<td>Amphotericin B</td>
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<td>Doxil</td>
<td>Doxorubicin</td>
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<td>Kaposi's sarcoma</td>
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<tr>
<td>DaunoXome</td>
<td>Daunorubicin</td>
<td>NeXstar Pharmaceuticals</td>
<td>Kaposi's sarcoma</td>
</tr>
</tbody>
</table>
pany Inc. (USA), and Sequus Pharmaceuticals Inc. (USA) are actively involved in the development of liposomal-based drug delivery systems.

Novasome lipid vesicles (Novavax, Inc., USA) are proprietary organized lipid structures in which drugs or other materials may be encapsulated for delivery into the body topically or orally. Novasome lipid vesicles are made using Novavax’s patented manufacturing process from a variety of readily available chemicals called amphiphiles, which include fatty alcohols and acids.

Micellar nanoparticles (Novavax, Inc.) are submicron-sized, water-miscible lipid structures that have different structural characteristics and are generally smaller than Novasome lipid vesicles. Micellar nanoparticles are derived from amphiphile molecules.

Proliposomes (ADD Drug Delivery Technologies AG) overcome the stability, entrapment, and production problems associated with conventional liposomal formulations. This approach avoids many difficulties encountered with the manufacturing of liposomes by forming liposomes at the point of delivery, presenting opportunities for novel delivery systems designed for dermal, mucocutaneous, pulmonary, oral, and parenteral use.

Stealth liposomes (Sequus Pharmaceuticals Inc., USA) are stable in plasma and avoid rapid removal from the bloodstream. This is achieved by attaching polyethylene glycol to the surface of the liposomes to form long-circulating liposomes. Stealth liposomes are large enough that typically they do not leak out of the bloodstream and into tissues through normal, healthy blood vessels. As a consequence, they continue to circulate intact until they reach tissues where new blood vessels form, such as tumors, sites of inflammation, and sites of injury.

Taste masking

Oral pharmaceuticals often impart an unpleasant taste, primarily bitterness. The desire for improved palatability in these products has prompted the development of numerous methods for taste masking, such as complexation of the drug with resins or cyclodextrins, use of microcapsules, particle coating, etc. Many of these contributions have been successfully commercialized in oral pharmaceutical preparations that are available over the counter or by prescription.

Chewable tablets (Elan Corporation) consist of a mild effervescent drug complex dispersed throughout a gum base. The drug is released from the dosage form as a result of physical disruption from chewing as well as chemical disruption from the interaction between the fluids in the oral cavity with the effervescent material. The taste of the compound is manipulated by a drug-coating technique that provides a physical barrier between the drug particles and the taste receptors of the mouth. These coating techniques are robust enough to withstand the mechanical onslaught caused by chewing so that taste masking is not compromised while patients take their medication.

KV Pharmaceuticals has developed a number of taste-masked technologies, including FlavorTech, a liquid formulation technology designed to reduce the bad taste of therapeutic products. Micromask is a taste-masking technology that incorporates a dry-powder, microparticulate approach to reduce objectionable taste by separating the unpleasant drug agent in a specialized matrix. Liquette is a taste-masking technology that incorporates unpleasant tasting drugs into a hydrophilic and lipophilic polymer matrix to suppress the taste. Oraquick is a technology in which the bitter taste of a drug candidate is first enhanced by neutralizing its negative taste characteristics and then developed into a quick-dissolving tablet formulation.

Tastemasking (Ascent Pediatrics Inc., USA) technology is used to mask the objectionable or unpleasant taste of various common ingredients used in pediatric pharmaceuticals.

Oral fast-dispersing dosage forms

A solid dosage form that dissolves or disintegrates rapidly in the oral cavity, resulting in a solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form. These are also known as fast-dissolving, rapid-dissolve, rapid-melt, mouth-dissolving, and quick-disintegrating tablets. Some of the advantages of oral fast-dispersing dosage forms include administration to patients who have difficulty in swallowing, more rapid drug absorption, patient convenience, and compliance. These dosage forms are particularly helpful for pediatric and geriatric patients who have difficulty in swallowing (dysphagia) and also for traveling patients, for whom water may not be easily or readily accessible. The technologies, some of which have been successfully marketed, mainly utilize conventional tableting processes with slight modification, freeze-drying methods, and floss-formation techniques for manufacturing.

EFVDAS or Effervescent Drug Absorption System (Elan Corporation) is a drug delivery technology that has been used in the development of a number of both OTC and prescription medications. This is particularly advantageous for conditions such as colds and flu, for which Elan has modified its EFVDAS technology to develop hot drink sachet products that combine medicines and vitamins for OTC use. The granular contents of the sachets can be added to boiling water to produce pleasant-flavored solutions. In these cases the effervescence of the granulate mixture is modified to accommodate the use of heated water. Examples of products that Elan has developed include effervescent ibuprofen, paracetamol (acetaminophen), cimetidine, naproxen, and a paracetamol and codeine combination product.

Fast Melt (Elan Corporation) is a highly porous, microfine matrix tablet. Once placed on the tongue, this matrix rapidly absorbs liquid and disintegrates. The drug, in a stabilized, size-reduced form to ensure optimal solubility, dissolves rapidly. The combination of a mild effervescent base and drug processing ensures that the dosage form goes into solution in approximately 15 to 30 seconds. The drug is released rapidly within the oral cavity, where it dissolves to form a drug solution that is then swallowed. This is particularly advantageous in cases like migraine where a fast onset of clinical effect is required. A portion of the drug solution may be absorbed locally in the oral cavity and therefore may avoid first-pass metabolism in the liver that limits the bioavailability of many drugs. The fast-melt system rapidly disintegrates in the oral cavity; hence, patients do not have to swallow large cumbersome dosage forms, which discourages many from taking their medication. Thus,
the fast-melt dosage form combines the benefits of liquid formulations with those of a solid oral dosage form.

**Flashdose** (Fuiz Technologies, USA) utilizes shearform technology to form a matrix known as floss. The floss is a fibrous material similar to cotton candy fibers and is commonly made from saccharides such as sucrose, dextrose, etc. The candy floss can then be milled and blended with active ingredients and other processing aids and subsequently compressed into fast-dissolving tablets.

**Flashtab** (Prographarm, France) is a combination of taste-masked multiparticulate active drug substances with specific excipients compressed into tablets. This orodispersible tablet is placed in the mouth, where it disperses rapidly before the patient swallows. Some of the drugs that are marketed using this technology are acetaminophen (pediatric and adult), ketoprofen, and ibuprofen.

**Multiflash** (Prographarm) is a multi-unit tablet composed of coated microgranules and fast-disintegrating excipients. This multiparticulate tablet quickly disintegrates in the esophagus after being swallowed with a minimum amount of water. This tablet avoids mucusal adhesion, and coated pellets can match various dissolution rates.

**Orasolv** (Cima Labs Inc., USA) is obtained by direct compression and utilizes effervescent materials (for faster disintegration) and taste-masking agents. The technique involves the formation of microcapsules by a novel technique involving the dispersion of active ingredient into a suitable polymer along with other excipients such as mannitol and magnesium oxide. The active agents and mannitol are added to the polymeric dispersion (ethyl cellulose, acrylates, etc.) under stirring, followed by the addition of magnesium oxide. Magnesium oxide and mannitol are added to promote the release of the active agent. The mixture is dried for one hour at 50 °C, delumped, and dried for another hour at the same temperature. The material is then screened (8-mesh) and dried for one hour at 60 °C. The formed microcapsules, effervescent mixtures, and other standard excipients are mixed and compressed to form tablets. The tablets have a hardness of about 1–2 kp and an in vivo disintegration time of <1 min.

**Wowtab** tablets (Yamanouchi Pharma Technologies, USA) are usually made by conventional tableting methods and have fast disintegration (1–40 s). The formulation usually consists of a mixture of fast-disintegrating but poorly compressible saccharides (e.g., mannitol, lactose, glucose, etc.) and a slowly disintegrating saccharide that shows good hardness upon compression (e.g., maltose, sorbitol, etc.). The mixture is compressed after undergoing a humidification and drying process resulting in tablets that show adequate hardness and rapid disintegration.

**Zydis** (R.P. Scherer, UK) uses freeze-drying technology in the manufacture of fast-disintegrating dosage forms. These formulations are combinations of watersoluble matrix material along with the drug and some functional excipients that are formed in the blister pockets and freeze-dried to remove the water by sublimation. The resulting structures are very porous in nature and rapidly disintegrate or dissolve upon contact with water. Some of the drugs that are being marketed in the form of Zydis products are oxazepam, lorazepam, piroxicam, loperamide, famotidine, loratidine, enalapril, phenylpropanolamine/brompheniramine, and selegiline.

**LYOC** (Farmalyoc, France) and **Quicksolv** (Janssen Pharmaceutica, USA) also utilize freeze-drying technology to produce oral fast-dispersing tablets.

### Technology for insoluble drugs

Drug solubility may be the rate-limiting step in absorption (e.g., in drugs belonging to Class 2 or drugs having good permeability but poor solubility) and therefore may affect the bioavailability of the drug. More than 40% of potential drug products suffer from poor water solubility. This frequently results in potentially important products not reaching the market or not achieving their full potential. A good deal of research has been done in this area, and currently a number of technologies are available to address the poor solubility of drugs.

**INDAS** or Insoluble Drug Absorption System (Elan Corporation) addresses the problem of poor solubility by manipulating the physicochemical characteristics of a drug to create a high-energy adsorbate that demonstrates enhanced solubility. This high-energy adsorbate is subsequently combined with Elan’s other controlled absorption technologies to deliver the required plasma profile. The drug in question, usually crystalline in nature, is converted into an amorphous form by a combination of energy, excipients, and unique processing procedures. Once the drug is converted to the desirable physical form, an adsorption process utilizing a novel polymer cross-linked technology prevents recrystallization and stabilizes the resulting high-energy complex. The combination of the change in the physical state of the drug coupled with the solubilizing characteristics of the excipients employed ensures that the solubility of the active ingredient is enhanced. Nifelan, a once-daily nifedipine formulation, is based on this technology and is marketed in Europe and Southeast Asia.

**Liquid-Oros** technology (Alza Corporation) is designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a self-emulsifying formulation system. It consists of an osmotic layer, which expands after coming into contact with water and pushes the drug formulation through an orifice in the capsule.

**NanoCrystal** technology (Elan Corporation) reduces a drug to extremely small particles (<400 nm in diameter) using a specialized milling technique. A suspension of the insoluble drug in a stabilizing solution, consisting of GRAS stabilizers and other excipients, is used for the milling process to prevent aggregation of the resulting nanoparticles and also serves to increase the dissolution rate of the nanoparticles by acting as a surfactant within the GI tract. Additionally, NanoCrystal technology serves as a platform for targeting drugs to specific anatomical sites or to control delivery over time. Once the NanoCrystal form of the insoluble drug has been transformed into a more physically stable form, it can be incorporated into other drug delivery systems such as oral controlled-release or highly concentrated parenteral solutions. Recently, Elan obtained marketing approval from FDA for a tablet form of American Home Products Corporation’s drug Rapamune, which represents the first approval for a
drug presentation containing NanoCrystal technology. Rapamune is indicated for the prevention of organ rejection in kidney transplant patients, and the new tablet provides easier administration and storage than the currently marketed Rapamune oral solution.

SoftGel (R.P. Scherer) is a soft gelatin capsule formulation that contains a high concentration of a hydrophobic drug in solution (or fine particles of drug in suspension) in a hydrophilic or lipophilic liquid. This technology has been specifically developed to improve the solubility, stability, bioavailability, and rate of absorption of drug molecules. ACT-3 (ibuprofen) marketed in Australia by Whitehall Laboratories (Australia), and Fortovase (saquinavir) marketed by Roche Labs, Inc. (USA) are some of the products based on this technology.

ADD Drug Delivery Technologies AG utilizes solubilizing properties of patented blends of phospholipids to increase solubility and bioavailability of poorly water-soluble drugs.

Colon-specific delivery
Although the small intestine is the primary site for drug absorption and is therefore a preferred area of the GI tract to target with various controlled-release technologies, considerable interest has been shown in the past few years in colon targeting of drugs. The main reasons for this interest are the reduced proteolytic activity in the colon, which may be advantageous in targeting certain drugs such as proteins and peptides that are enzymatically degraded in the stomach or small intestine, and the topical treatment of carcinomas and inflammatory bowel diseases. In the past few years many colon-specific dosage forms have been developed, including prodrugs, cross-linked hydrogels, matrices, and coated dosage forms. Coated dosage forms are preferred because of innovations in the coating technology and wide flexibility in the design. These coated dosage forms are mainly based upon one of the following:

- The pH-controlled release coatings that are insoluble at the lower pH of the stomach and dissolve in the lumen of the small intestine. To achieve release in the colon, the start of the drug release is controlled by increasing the thickness of the coating, allowing a pH- and time-controlled polymer dissolution and drug release. These pH-sensitive enteric polymers dissolve in a pH between 6 and 7 and thus release the drug as soon as the pH of the intestine reaches 6 or 7. Some of these enteric polymers are cellulose acetate phthalate, HPMC phthalate, and Eudragit L and S.
- Time-controlled release coating in which the lag time depends upon coating thickness and drug release can be accomplished by changes in osmotic pressure or disruption of the coating by swelling of the core.

Oros-CT (Alza Corporation) is a system that can be used as a once- or twice-a-day colon-targeted dosage form and is based on the principles of osmotic pressure. Oros-CT can be a single osmotic unit or can be comprised of as many as five to six push-pull osmotic units filled in a hard gelatin capsule. Each bilayer tablet consists of an upper compartment (drug along with osmotic agents) and a lower compartment (polymeric osmotic agent), surrounded by a semipermeable membrane. An orifice is created in the membrane next to the drug layer. After coming into contact with the GI fluids, the gelatin capsule dissolves and the enteric coating prevents entry of water from the stomach. As the system enters into the small intestine, the enteric coating dissolves and water is imbied into the core, thereby causing the push compartment to swell. At the same time, flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate that is precisely controlled by the rate of water transport across the semipermeable membrane.

Pulsincap (R.P. Scherer) consists of a water-insoluble capsule body and a water-soluble cap. The drug formulation is contained inside the capsule. The soluble cap dissolves in the intestine, thereby allowing the hydrogel plug to swell and expand. Ejection of the swollen plug occurs after a lag time that depends on the hydrogel plug, the length of the plug, and the fit ratio (plug diameter to body diameter).

Colon Specific Systems (Advanced Polymer Systems, Inc.) uses Microsponge systems to protect the active agent from the environment of the stomach and delivers the drug to the colon in a controlled fashion.

Intranasal delivery
Intranasal delivery of certain drugs offers significant advantages. The nasal cavity can be used for the delivery of several compounds and offers rapid absorption into the systemic circulation, providing rapid onset of desired therapeutic effect, lower required dosages, fewer side effects, and improved patient compliance. Moreover, this route may also permit the delivery of challenging molecules such as proteins and peptides.

In the past drops were instilled in the nose, but with the advent of insufflator technology, drops are seldom used now. Nasal dosage forms consist mainly of preparations containing dispersed or dissolved drugs placed in a container that is squeeze- or spray-activated. Alternatively, liquid solutions can be delivered using metered atomizing pumps or metered-dose pressurized nasal inhalers. Butorphanol (Stadol NS Nasal Spray, Bristol Myers Squibb Co., USA), calcitonin (Miacalcin Nasal Spray, Novartis), dihydroergotamine (Migranal Nasal Spray, Novartis, Inc.), sumatriptan (Imitrex Nasal Spray, GlaxoSmithKline), and desmopressin (DDAVP Nasal Spray, Aventis Pharma, USA) are some of the drugs marketed in the form of a nasal spray. Cromolyn sodium (Nasal-crom Nasal Solution, Fisons Pharmaceuticals) is available in a solution form. Budesonide (Rhinocort Nasal Inhaler, Astra) and beclomethasone dipropionate (Rino Clenil, Chiesi Farmaceutici) are marketed in the form of metered-dose pressurized aerosols. Beclomethasone dipropionate is also available in the form of a metered-dose manual spray unit (Becconase AQ, GlaxoSmithKline, and Venckenase AQ, Schering Plough Corporation).

Nasal powders are an alternative dosage form and may show improved stability. Administration of powders requires nasal insufflators that are either mechanically or respiration actuated. In mechanical devices, a rubber bulb is connected through the dose reservoir to a nasal adapter. Squeezing the rubber bulb provides a stream of air that is capable of emitting the loaded powder in the insufflator. Rinoflatore (Fisons, Italy), Miat Nasal Insufflator (Miat, Italy), and Puvlizer (Teijin, Japan) are some of the marketed insufflators for nasal administration of
powders. Respiration-actuated devices are a nose-adapted version of dry powder inhalers (DPIs). With both types of devices, the drug is loaded in a gelatin capsule that is pierced just before activation. The capsule is located between the air jet producer and the nose adapter, and the flowing airstream creates turbulence inside the capsule, which aerolizes and releases the powder from the capsule.

Nasal gels also can be used to provide an enhanced bioavailability compared with oral delivery. EnerB (Nature’s Bounty, Inc.), a vitamin B-12 dietary supplement, is available in gel form.

Pulmonary delivery
Until now, pulmonary delivery has been used primarily for the treatment of respiratory disease. More recently, the lung’s natural ability to transfer molecules into the bloodstream has been utilized for delivering drugs to the systemic circulation. This method is a noninvasive alternative to painful injections and can lead to the rapid onset of action and good bioavailability. Inhalation devices broadly fall into three categories: pressurized metered-dose inhalers (MDIs), nebulizers, and DPIs. MDIs contain the drug as a solution or a suspension of fine particles in a liquefied propellant held under high pressure. The drug is emitted through an orifice from a metering valve. Nebulizers, on the other hand, do not require propellants and can generate large quantities of small droplets capable of penetrating into the lung. Recently, a great deal of work has been done in the field of DPIs. In DPIs, the drug is stored in a dry state, thereby ensuring long-term stability and sterility.

Some of the single dose breath-driven DPIs that are currently marketed are Rotahaler (GlaxoSmithKline), Flowcaps (Hovione), and Cyclohaler (Pharmachemie). Diskhaler and Accuhaler (GlaxoSmithKline) are multidose factory-metered inhalers. In addition, several multidose patient/device-metered DPIs are available; Clickhaler (M L Labs), Easyhaler (Orion), Pulvinal (Chiesi), Turbohaler (AstraZeneca), and Ultrahaler (Aventis Pharma).

AERx system (Aradigm Corporation, USA) is based on aerosol-generation technology capable of producing low-velocity small particles suitable for efficient and reproducible pulmonary delivery. The system aerosolizes liquid formulations that are prepackaged in unit-dose packets for inhalation. Each unit-dose packet consists of a small blister package that stores a liquid drug formulation and an aerosolization nozzle with a membrane incorporating an array of micro-machined holes. The AERx device creates a respirable aerosol by releasing a mechanical actuator that is activated automatically when the patient’s inhalation is optimal for drug delivery. The actuator compresses the blister packet, thereby forcing open the sealed channel and extruding the liquid drug through the aerosolization nozzle. The aerosolized drug produced by this process is inhaled through the mouthpiece of the AERx device. The aerosolization of the liquid drug via the disposable nozzle takes about 1 s and produces a low-velocity, fine-particle aerosol necessary for optimized deposition within the lungs.

Spiros (Dura Pharmaceuticals Inc., USA) is designed to deliver a relatively consistent drug dose to the lungs over a wide range of inspiratory flow rates. The core technology contained in Spiros is an aerosol generator that uses electro-mechanical energy to disperse drug powder to form an aerosol for inhalation. The main components of the aerosol generator include the impeller, the motor, the breath-actuated switch, and the dosing chamber. When the switch is activated, the electric circuit is completed and the impeller rotates. The action of the impeller on the dry powder formulation supplies the energy to disperse the drug and provides a zero-velocity cloud of aerosolized drug for inhalation. The cloud of aerosolized drug is suspended in the dosing chamber and is delivered to the lungs only as the patient inhales.

Vaginal/rectal delivery
The vagina has been studied as a favorable site for the local and systemic delivery of drugs, and this route offers certain advantages such as the avoidance of the gut and hepatic first-pass metabolism, reduction in gastrointestinal and hepatic side effects, and local targeting of drugs to the reproductive organs. Vaginally administered agents and formulations are being developed mainly to provide dual prophylaxis for contraception and protection against microbial infections, including AIDS and other sexually transmitted diseases. This route also has potential for uterine targeting by the so-called first uterine pass effect of active agents such as progesterone and danazol.

Hycore-V (Core Group Plc, Scotland) uses hydrogel polymer technology to absorb fluid and swells without losing its physical form. As the hydrogel swells, the drug is released in a controlled manner. Drug release can be controlled over a period of a few hours to several days by varying the shape and the physical and chemical properties of the polymer. Hycore-V is delivered through the vagina in the form of a pessary. Hycore-R (Core Group Plc) uses similar technology and delivers the drug through the rectum in the form of a suppository.

Vagisite (KV Pharmaceuticals) is a semi-solid system intended for drug administration within the vaginal vault. Biosert (KV Pharmaceuticals) is a bioadhesive controlled-release system that is a solid rectal or vaginal suppository at room temperature and, after insertion, becomes a bioadhesive long-acting cream.

Site-specific drug delivery
One of the goals of effective drug delivery is to control and optimize the localized release of drug at the target site and rapidly clear the nontargeted fraction. In the past few years, there has been considerable interest in the development of a delivery system that will release the drug locally in a highly selective fashion. Some of the benefits of this type of delivery system are the delivery of a calculated amount of drug at the site of action and limited access to other organs. The amount of drug reaching the systemic circulation theoretically will be less, thereby resulting in fewer side effects. At present, a number of technologies are available for site-specific delivery.

Atrigel (Atrix Laboratories, Inc., USA) comprises biodegradable polymer formulations that are administered as flowable compositions (solutions, gels, pastes, and putties) that solidify in situ upon contact with body fluids to form biodegradable implants. The Atrigel system is designed to provide extended localized or systemic drug delivery in a single application without the need for surgical implantation or removal.
Durasite (Insite Vision Inc., USA) is an eye drop formulation comprised of a cross-linked carboxy-containing polymer that incorporates the drug to be delivered to the eye.

Matrix Delivery System (Matrix Pharmaceuticals, USA) is an aqueous-based protein system in which a chemotherapeutic drug is combined with a protein matrix and a vasoconstrictor to create an injectable gel. This gel enables targeted delivery of water-soluble drugs by direct injection into solid tumors and skin lesions. The Matrix delivery system localizes the release of the drug, maintaining high drug concentrations at the tumor or lesion site and increasing the duration of exposure of the targeted tissue to the therapeutic agent.

Microsphere Delivery System (Core Group Plc) uses biodegradable polymers and a method that facilitates the microencapsulation of water-insoluble and water-soluble compounds. Potential applications of this technology include the long-term controlled delivery of injectable compounds, the delivery of active agents to sites poorly accessible from systemic circulation, and site delivery of highly potent agents.

Oligosphere Injectable Microspheres (Macromed, Inc.) is a proprietary polymeric microsphere technology based on FDA-approved PLGA polymers. MacroMed’s patented processing uses aqueous co-solvents providing a drug-friendly loading environment. MacroMed’s process also creates a homogenous drug/polymer matrix. This enables a constant release profile with little or no initial burst. Oligosphere is injected parenterally and is designed for drug release profiles of greater than one month.

ReGel Injectable Controlled-Release System (Macromed, Inc.) is designed to deliver active agents systemically or locally for periods of one to six weeks. MacroMed formulates these systems with its proprietary thermosensitive and biodegradable class of hydrogels. These formulations are a liquid at or below room temperature and are injectable through a small 25-gauge needle. Upon injection as a liquid, the product quickly becomes a gel at body temperature, forming a depot that slowly degrades over a period of four to six weeks. The ReGel System is biodegradable and is made from GRAS components.

ReGel’s solubilizing characteristics have been shown to increase syringability and consistency of dose.

Retinal delivery system (Insite Vision, Inc.) is a device that provides controlled nonsurgical delivery of ophthalmic drugs to the retina and other tissues in the posterior chamber of the eye.

Oral transmucosal delivery
Oral transmucosal systems address the need for a convenient noninvasive drug delivery vehicle that provides rapid onset of therapeutic action and allows the patient to control drug administration until the desired effect is achieved. The drug is released in the mouth, allowing rapid absorption through the oral mucosal tissues.

Bioadhesive Delivery System (Columbia Laboratories, Inc., USA) consists of a polymer, polycarbophil, and an active ingredient. This system is based on the principle of bioadhesion, a process by which the polymer adheres to epithelial surfaces and to mucin, a naturally occurring secretion of the mucus membranes. The polymer remains attached to epithelial surfaces and the mucin and is discharged upon normal cell turnover or upon the detachment of the mucin from the mucus membranes, a physiological process that, depending on the area of the body, occurs every 12 to 72 h.

Oral transmucosal delivery (TherTech, Inc.) may enable the delivery of many large-molecule drugs, including peptides and polysaccharides that cannot readily be delivered orally or transdermally. TherTech’s oral transmucosal delivery systems are solid dosage forms that will adhere to various surfaces in the oral cavity and deliver drugs within a period of time.

Future directions and conclusions
As discussed in this article, drugs can be delivered to a patient by many different delivery systems, including oral, transdermal, injection, implants, etc. Most of the drugs are amenable to these types of delivery systems. With the sequencing of the human genome, biotechnology companies are rapidly developing a large number of peptide- and protein-based drugs. It is expected that in the next 10 to 20 years, protein- and peptide-based drugs will constitute more than half of the new drugs introduced into the market, and more than 80% of these protein drugs will be antibodies. These biopharmaceuticals (proteins, peptides, carbohydrates, oligo-nucleotides, and nucleic acids in the form of DNA) present drug delivery challenges because these are often large molecules that degrade rapidly in the bloodstream. Moreover, they have a limited ability to cross cell membranes and generally cannot be delivered orally. Such molecules will be much more difficult to deliver via conventional routes, and injections may be the only means of delivery (at least as of today).

The routes of administration will be dictated by the drug, disease state, and desired site of action. Some sites are easy to reach such as the nose, the mouth, and the vagina. Others sites are more challenging to access, such as the brain. Gene therapy is also likely to be one of the most exciting growth sectors as biotech companies become involved in drug delivery. Currently, no product in this category, which includes genetically engineered cells, has reached the market but several are in Phase III clinical trials. By 2005, some of these products will reach the market, and their value has been estimated to be close to $5 billion.

In conclusion, the market for drug delivery systems has come a long way and will continue to grow at an impressive rate. Today’s drug delivery technologies enable the incorporation of drug molecules into new delivery systems, thus providing numerous therapeutic and commercial advantages. A large number of companies are involved in the development of new drug delivery systems, which is evident by an increased number of products in the market and the number of patents granted in the recent past. Tomorrow’s drugs definitely will be more challenging in terms of the development of delivery systems, and pharmaceutical scientists will have to be ready for a difficult task ahead.

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Suggested reading
3. S.V. Sastry, J.R. Nyshadham, and J.A. Fix, “Recent Technological Advances in Oral Drug