10 ROUTES OF DRUG DELIVERY

Any biological membrane in the human body is a potential portal for drug delivery. Thus, drugs can be delivered by various routes, such as ophthalmic, nasal, buccal, sublingual, respiratory, oral (GI tract), transdermal, parenteral, implantable, intrauterine, and rectal routes. Each delivery route has its advantages and limitations. The best delivery route for a particular drug depends on many factors and we will discuss several delivery routes most widely used for the development of controlled-release dosage forms.

I. ORAL CONTROLLED-RELEASE DOSAGE FORMS

The oral route is the most convenient route of administration. All a patient has to do is swallow the oral dosage form. Oral dosage forms provide a multitude of advantages. One example is the oral polio vaccine. Polio was a scourge that afflicted nearly 58,000 at its peak in 1952 in the United States. Its suffering was alleviated only with an injectable vaccine developed by Dr. Jonas Salk in the mid-1950s and an oral polio vaccine by Dr. Albert Sabin in the early 1960s. The oral vaccine was immensely popular with parents and pediatricians. The oral polio vaccine does not involve needles that are often scary enough to make children cry. Not only that but oral vaccination makes mass vaccination easier. Furthermore, oral polio vaccination costs less than vaccination by injection ($2.85 versus $6.54 per dose) (Kaplan & Hanchette, 1998).

Since oral delivery is the most preferred route of drug delivery, choosing other routes of delivery requires good reasons, such as problems in absorption, metabolism, or local intolerability by oral delivery. Because a drug released from an oral dosage form has to be absorbed from the GI tract to have a pharmacological effect, the drug response by oral administration is rather slow. This, however, does not appear to be a problem for most drugs since a majority of drugs are administered by oral route. Except for life-threatening situations, oral administration will work fine for most cases. However, this does not mean any drug can be delivered by oral routes. In the development of oral controlled-release dosage forms we have to consider unique properties of the GI tract.

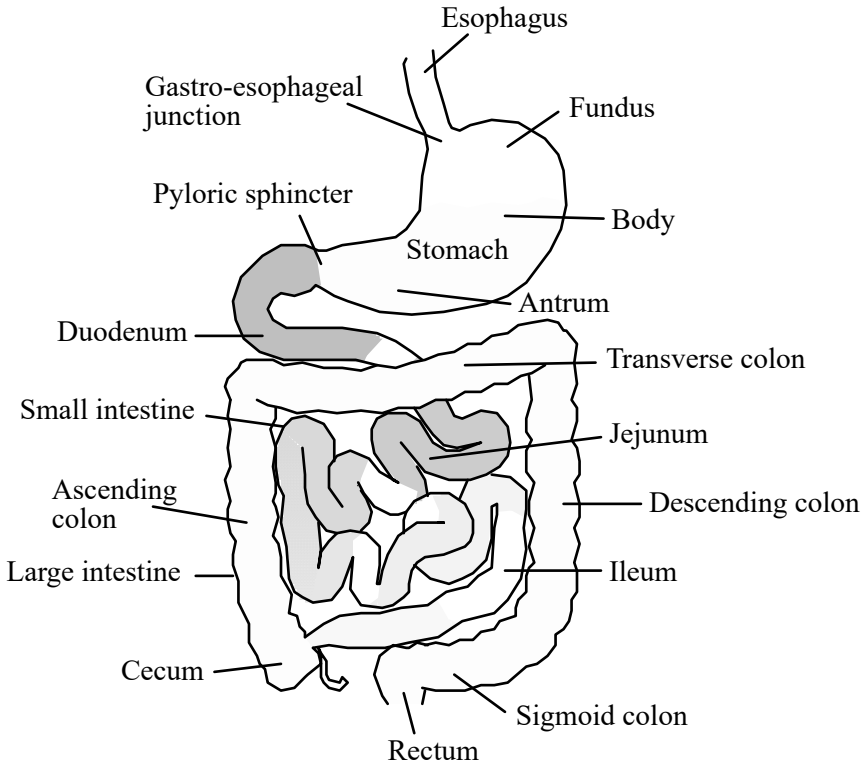


Figure 10.1 Schematic description of the GI tract. The absorption abilities of the different segments of the GI tract for most drugs are shown with different gray scales (the darker the region, the more absorption of the drug).

A. Limiting Factors for Oral Controlled-Release Dosage Forms

There are a few unique properties of the GI tract that make development of oral controlled-release dosage form rather difficult. Figure 10.1 shows a schematic description of the GI tract.

1. Relatively Short Gastric-Emptying and Intestinal-Transit Times

Although the current controlled drug-delivery technology is such that one can prepare oral dosage forms that deliver a drug over days to years, no oral controlled-release dosage forms can deliver drugs such a long period of time. This is simply because all oral dosage forms will be removed from the GI tract after a day or so. Table 10.1 shows the residence times of both liquid and solid foods in each segment of the GI tract. The values in Table 10.1 should be taken as relative, rather than absolute, and are intended to point out general differences among different segments in the GI tract. Gastric-emptying time ranges from 10 min to about 3 h depending on many factors. Gastric emptying from the stomach varies 0.5–2 h in the fasted state (Davis, Hardy, & Fara, 1986). The presence of food in the stomach tends to delay the gastric emptying. In the fed condition, larger dosage forms exit after the meals have emptied while small pellets empty with the meal (Feldman, Smith, & Simon, 1984; Meyer *et al*., 1985). The type of food has a strong influence on the gastric emptying time. Carbohydrate and proteins tend to be emptied from the stomach in less than an

hour, while lipids can stay in the stomach for more than an hour. Thus, depending on the quantity and the type of food that a patient has, the gastric-emptying time is altered. Many other factors may affect the gastric-emptying time including disease state or various drugs (Berner & Kydonieus, 1996).

Table 10.1 Transit Time in Each Segment of the GI Tract.

Segment	Type of food	
	Liquid	Solid
Stomach	10–30 min	1–3 hr
Duodenum	< 60 s	< 60 s
Jejunum & Ileum	3 ± 1.5 h	4 ± 1.5 h
Colon		20-50 hr

The small-intestinal transit time is more reproducible and is typically about 3–4 hours (Read *et al*., 1986). Thus, the transit time from mouth to cecum (the first part of large intestine) is 3–7 h. Colonic transit is highly variable and is typically 10–20 h (Hardy *et al*., 1988). Since most drugs are absorbed from the small intestine, the time interval from mouth to cecum for oral controlled-release dosage forms is too short, unless the drug can be equally well absorbed from the large intestine. Thus, most of the oral controlled-release dosage forms can be effective for only about 8 h. If the drug can be absorbed from the large intestine, the time interval for drug absorption can be increased to 1 d. Thus, certain drugs can be delivered for 24 h by a single administration of an oral controlled-release dosage form. But many drugs require more than one administration. The study on the GI transit time of once-a-day OROS® tablet showed that the median total transit time was 27.4 h with a range of 5.1–38.3 h (John *et al*., 1985).

2. Non-uniform absorption abilities of different segments of the GI tract.

The performance of the oral dosage form profoundly depends on the transit through the GI tract because the extents of drug absorption from different regions of the GI tract are different. Drug transport across the intestinal epithelium in each segment is not uniform, and it tends to decrease as the drug moves along the GI tract. If a drug is absorbed only from the upper segment of the GI tract, it is known to have a "window for absorption." For this reason, the rate and the extent of drug absorption depends on the residence time of the dosage form within each segment of the gut. One of the difficulties in designing controlled-release or targeting systems for oral use is that once a conventional tablet or capsule is swallowed, control over its movement and position in the GI tract is lost. Furthermore, for those drugs with window for absorption, no demonstrable advantages can be observed with controlled-release dosage forms. Clearly, for oral controlled-release dosage forms to be effective, some control over the GI transit time is required (Florence, 1993).

To compensate the decrease in the drug absorption abilities owing to the window for absorption, an oral dosage form needs to release more drug as it passes through the GI tract. Nisoldipine Coat-Core (CC) controlled-release formulation was developed to optimize the drug's time-effect profile over the 24-h dosing interval. On contact with water in the upper GI tract, where absorption is naturally fast, the tablet coat slowly erodes, producing a controlled, sustained release of the drug. Once the erosion process reaches the core, the tablet has moved to the colon, where the absorption rate is decreased and the remaining portion of the total dose is released at a higher rate owing to the immediate-release characteristics of the tablet core, avoiding nonabsorption from fecal secretion. Thus, blood levels remain relatively constant with a once-daily dose (Riley & DeRuiter, 1996).

3. Presystemic Clearance

Even with drugs that can be absorbed equally well throughout the GI tract, pre-systemic clearance may occur in some sites of the GI tract and this may result in non-uniform absorption. Degradation of orally administered drugs can occur by hydrolysis in the stomach, enzymatic digestion in the gastric and small intestinal fluids, metabolism in the brush border of the gut wall, metabolism by microorganisms in the colon, and/or metabolism in the liver prior to entering the systemic circulation (*i.e.*, first-pass effect). Such degradations may lead to highly variable or poor absorption of drug into the systemic circulation. For example, metoprolol is absorbed equally well from the large intestine, but pre-systemic clearance occurs in the large intestine. As shown in Figure 10.2, the systemic availability of metoprolol is lower for the OROS® device, which delivers the drug at a zero-order rate, compared with intragastric infusion owing to the transit of

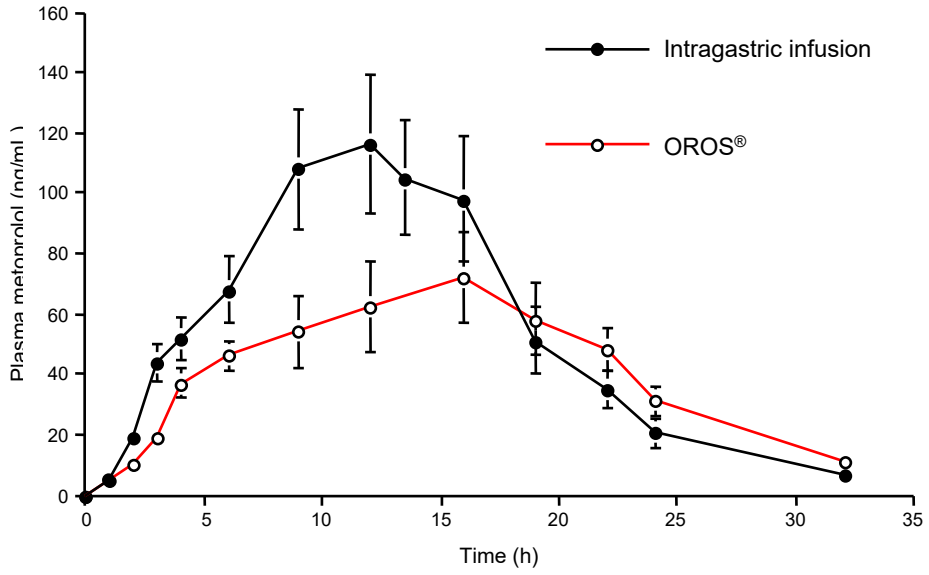


Figure 10.2 Mean plasma profiles of metoprolol after single oral dosing of metoprolol OROS® (with 190 mg of metoprolol fumarate and release rate of 14 mg/h) and intragastric infusion for 13.5 h.

the OROS® device to the colon. Digoxin is also known to undergo microbial metabolism before absorption. For this type of drugs, of which presystemic clearance is determined by the site of absorption, systemic availability is enhanced when drug delivery is restricted to the upper segment of the gut, or to the stomach.

4. Poor Absorption of Peptide and Protein Drugs

The full exploitation of biotechnology products, such as peptides and proteins, lies on the industry's ability to deliver them orally. Unfortunately, it is virtually impossible to delivery high molecular-weight drugs, such as peptide and protein drugs, through the oral route. First of all, peptide and protein drugs are unstable in the harsh conditions in the GI tract and degraded by enzymes. The protein function follows the form and changing the three-dimensional structure of a protein too radically may cause loss of the protein's function. Even if protein structures are maintained, absorption of high molecular-weight drugs (*e.g.*, insulin) through the epithelial cells of the GI tract is very difficult at best. The GI tract is not designed to absorb intact peptides and proteins.

A variety of approaches, mostly proprietary techniques developed by new companies, have been used and claimed to be effective in oral delivery of peptide and protein drugs. Sodium *N*-(2-hydroxybenzoyl)aminocaprylate (SNAC) was used to prepare oral dosage forms for the delivery of macromolecular drugs, such as interferon, recombinant human growth hormone (rHGH), insulin, vaccines, and heparin by Emisphere Technologies, Inc. A lipid technology, Macrosol™ technology developed by Cortecs in United Kingdom, was claimed to deliver calcitonin and insulin by oral administration. Whatever the novel technology may be, its success should be determined by the ability of delivering the accurate amount of drugs using a clinically acceptable delivery mode. Simply showing the possibility is not enough. The possibility of delivering insulin by oral administration does not mean anything, since delivery of the exact amount of insulin in a reproducible manner is required.

5. Poor *in vitro-in vivo* Correlation

Prediction of *in vivo* availability using simple *in vitro* tests would be most useful in developing new dosage forms with desired *in vivo* performance and evaluating potential bioavailabilities of different formulations or different lots of the same formulation as a quality control. *In vitro* dissolution tests have been used as the sensitive and reliable predictors of *in vivo* availability. While official *in vitro* methods (*e*.g., disintegration and dissolution tests) have great practical values, they do not permit prediction *in vivo* availability reliably; thus, they cannot replace *in vivo* availability studies (Banakar & Makoid, 1996). Establishing *in vitro-in vivo* correlation is important.

B. Once-a-Day (or Once-Daily) Oral Dosage Forms

In general, most drugs administered by oral route have to be delivered a few times a day owing to the limitations described above. However, in

many cases, drugs can be made once-a-day (or once-daily) dosage forms without any particular efforts of developing controlled-release dosage forms. This is possible not only for drugs with long half-lives but also with those with very short half-lives.

1. Drugs becoming Active Metabolite with Long Half-Lives

Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic activity. Loratadine is rapidly absorbed following oral administration with times to maximum concentration (t_{max}) of 1.3 h for loratadine and 2.5 h for its major active metabolite, descarboethoxyloratadine. The mean elimination half-lives in normal adult subjects were 8.4 h (ranging 3–20 h) for loratadine and 28 h (ranging 8.8–92 h) for descarboethoxyloratadine. The considerable variability in the pharmacokinetic data may be due to the extensive first-pass metabolism. Owing to the long half-life of descarboethoxyloratadine, loratadine tablets, syrup, and rapidly-disintegrating tablets (Claritin®) can be used only once-a-day. Claritin-D® 24-h extended-release tablets are also available. The extended-release formulation is for another active ingredient, pseudoephedrine sulfate, which does not have a long half-life.

Sibutramine hydrochloride monohydrate (Meridia® from Knoll Pharmaceutical Co.) is used for weight control by once daily dosing. Sibutramine is rapidly absorbed from the GI tract (t_{max} 1.2 h) following oral administration and undergoes extensive first-pass metabolism in the liver (oral clearance of 1750 L/h and half-life of 1.1 h) to form the pharmacologically active mono- and didesmethyl metabolites M_1 and M_2. Peak plasma concentrations of M_1 and M_2 are reached within 3–4 h. An *in vitro* study showed that sibutramine, M_1, and M_2 are extensively bound (97%, 94%, and 94%, respectively) to human plasma proteins at plasma concentrations seen following therapeutic doses. The elimination half-lives of M_1 and M_2 are 14 h and 16 h, respectively. With such long half-lives, no controlled-release formulation is necessary to make once-daily dosage forms.

Troglitazone (Rezulin® from Parke–Davis Pharmaceuticals, Ltd.) is an oral antihyperglycemic agent for managing type-2 diabetes (non-insulin-dependent diabetes mellitus, or adult-onset diabetes) primarily by decreasing insulin resistance. Troglitazone is a thiazolidinedione antidiabetic agent that lowers blood glucose by improving target-cell response to insulin. It is thought to bind to nuclear receptors peroxisome proliferator activated receptor (PPAR) that regulate the transcription of a number of insulin responsive genes critical for the control of glucose and lipid metabolism (Parke–Davis, 1999). Troglitazone is absorbed rapidly following oral administration, and the maximum plasma concentration (t_{max}) occurs within 2–3 h. Once absorbed, it is extensively (> 99%) bound to serum albumin. Mean plasma elimination half-life ranges 16–34 h. Because of such a long half-life, troglitazone is administered orally once-a-day.

2. Drugs with Short Half-Lives

Prilosec® (omeprazole) delayed-release capsules from Astra Merck are indicated for short-term treatment of active duodenal ulcer. Omeprazole is acid-labile and thus it has to be enteric coated and is supplied as delayed-release capsules for oral administration. In healthy subjects, the plasma half-life is 0.5 –1 h. After rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more. In the gastric mucosa, omeprazole suppress gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretary surface of the gastric parietal cell. After oral administration, the onset of the antisecretory effect of omeprazole occurs within 1 h, with the maximum effect occurring within 2 h. Inhibition of secretion is about 50% of maximum at 24 h and the duration of inhibition lasts up to 72 h. Despite the very short plasma half-life, the antisecretory effect last more than 24 h apparently owing to prolonged binding to the partial H^+/K^+ ATPase enzyme.

C. Design Parameters for Oral Controlled-Release Dosage Forms

1. Dose Size

The size of the dose is an important factor that presents a very practical problem. Single dose size of 500 mg for the conventional dosage form is an upper limit for the controlled release system. If the single dose size is larger than 500 mg, the total amount and the volume of the controlled release system becomes too large.

2. Drug Molecular Size

Drug molecules must diffuse through a polymeric membrane or matrix to be released. As we discussed previously, diffusion of drug molecules through the solution-diffusion membranes depends on the molecular weight of the drug. Drugs with molecular weight smaller than 750 Da are preferred. Diffusion coefficient of about 10^{-8} cm^2/s is desired for substances with intermediate molecular weights (150–400 Da).

3. Charge and pK_a of a Drug

The uncharged form of a drug is preferentially absorbed through the cellular membrane. For charged drugs, the pH of the environment is important. The values of pH in the duodenum and ileocecal junction are 5.8 ± 0.8 and 6.5–8.5, respectively (Mojaverian *et al*., 1989). The pH near the jejunal membrane may be as low as 6.1 compared to 7.2 in the bulk (Lucas, 1983). Charge and pK_a of a drug are also related to water solubility and thus they affect diffusion through the polymeric membranes.

4. Aqueous Solubility

The lower limit on solubility for controlled release system is 0.1 mg/mL. Drugs with lower solubility cannot be used for the diffusion-controlled dosage forms because of small driving force for diffusion.

Absorption of a drug with low solubility is often limited by dissolution rate. Examples are digoxin, warfarin, diazoxide, griseofulvin, and salic-

ylamide. In general, the drugs with solubility less than 0.01 mg/mL show dissolution-limited availability and thus have inherent controlled-release property.

Drugs with high solubility are difficult to deliver in controlled-release dosage forms. Highly water-soluble drugs have small partition coefficients into the hydrophobic cell membranes, and as a result, they are not absorbed very well. This means that the drug absorption is controlled by the cellular absorption of the drug rather than by the release from the dosage forms.

Drugs with pH-dependent solubility present difficulties in the delivery. Tetracycline dissolves to a greater extent in stomach than in the intestine, but the maximum absorption of tetracycline occurs in the intestine.

Different polymorphic forms of the same drug have different solubilities, which results in different absorption properties and as a result different bioavailability.

5. Partition Coefficient

Drug molecules that are released from an oral controlled-release dosage form have to be absorbed to be effective. For absorption to occur from the GI tract, drug molecules have to penetrate through the cellular membranes. The drug absorption through the cells is known to be related to the partition coefficient (K). In this case, the partition coefficient is measured using water and *n*-octanol. $K = C_o/C_w$, where C_o and C_w are drug concentrations in *n*-octanol and water, respectively.

Increase in K leads to increased absorption, but it also leads to low solubility. Thus, prodrug approach is used. A prodrug is a compound resulting from chemical modification of a pharmacologically active compound that will liberate the active compound *in vivo* owing to enzymatic or hydrolytic cleavage (Ranade & Hollinger, 1996). The primary purpose of employing a prodrug is to increase intestinal absorption or to reduce local side effects, (*e.g.*, aspirin irritation). For this reason, a prodrug is not generally classified as a sustained-release mechanism. However, reversible modification of the physicochemical properties of a drug results in better intestinal transport properties and hence influences the blood-drug concentration-time profile. Thus, prodrugs 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 reported.

6. Stability

Drugs unstable in the stomach (*i.e.*, acid-labile drugs) cannot be delivered in the stomach. Drugs unstable in the GI tract cannot be delivered by oral administration. Insulin is degraded in the GI tract and thus cannot be delivered by oral route. Even if insulin is not degraded by enzymes, it is too

big to be absorbed through the cell membranes. Drugs that are degraded in the GI tract may undergo more degradation when slowly released from the controlled release dosage forms. Metabolism of alprenolol during the passage through the intestinal wall was more complete with sustained release form than the conventional dosage form.

7. Half-Life

In general, drugs with very short or long half-lives are poor candidates for oral controlled-release dosage forms (Madan, 1985a). Drugs with short half-lives will require too much amounts for the controlled-release dosage forms. The drugs with short half-lives are furosemide (about 30 min), levodopa and penicillin G (about 45 min), cephalexin and propylthiouracil (about 1 h), and ampicillin and cloxacillin (about 1.5 h) (Madan, 1985a). Drugs with long half-lives do not need controlled-release dosage forms. They are inherently sustained release. For example, the half-life of phenylbutazone is 72 h and this certainly does not need long-acting controlled-release dosage forms. Check the half-life of digoxin and determine whether it is useful to deliver digoxin in a controlled release dosage form. The optimum half-life for controlled-release dosage forms is about 4 h for a 12 h release controlled release product. Propranolol, propoxyphene, and procainamide are examples.

One thing to be cautioned here is that some drugs have extended pharmacological effects even though their half-lives are short. Reserpine has a half-life of 15 min, and yet its activity persists for as long as 48 h. This is due to irreversible inhibition of monoamine oxidase by reserpine and reproduction of new enzymes by the body (Madan, 1985a; Levine & Sjoerdsma, 1963). Prednisone and methyl prednisolone have biological half-lives of 1.0 h and 3.3 h, respectively. Yet, their antiinflammatory effect persists for up to 36 h (Madan, 1985a). In these cases, long-term controlled-release delivery systems may be not only therapeutically unnecessary but also harmful because of potential side effects.

8. Clinical Response

If the difference in drug effect between the conventional and the controlled-release dosage forms are not great, then the higher cost of making controlled-release dosage forms can be a problem.

9. Drug-Food Interactions

Taking tetracycline-type drugs with milk or dairy products reduces bioavailability.

10. Therapeutic Index

Drugs with narrow therapeutic index require precise control over drug concentration. For accidental overdosing or drug leaking, it takes longer time to retrieve the dose from the body with controlled-release dosage forms than with the conventional dosage forms.

Table 10.2 Devices used as Platforms for Gastric Retention

Intragastric floating systems (low density systems)
High density systems
Mucoadhesive systems
Unfoldable, extendible, or swellable systems
Superporous hydrogel systems

D. Methods of Extending Gastric Retention Time

The drug absorption rates are best maintained by a delivery device that releases the drug at its optimum absorption site. Since most drugs absorbed in the upper small intestine, the absorption of the drugs will be improved if the oral controlled-release dosage forms are maintained in the stomach. Thus, as long as a drug is stable in acidic environment, drugs can be delivered for longer period of time than allowed by the conventional oral dosage forms. The approaches that have been used to achieve long-term gastric retention, although with limited successes, are listed in Table 10.2.

1. Intragastric Floating Systems (Low-Density Systems)

The main idea of preparing floating oral dosage forms is to make the dosage forms with a density less than 1 so that they can float on top of the gastric juice. The devices may acquire low density after administration to the stomach (Figure 10.3a) or possess low density from the beginning (Figure 10.3b).

a. Hydrodynamically-Balanced Intragastric Delivery System™ (HBS)

The hydrodynamically-balanced gastrointestinal drug-delivery system, in either capsule or tablet form, is designed to prolong GI residence time in an area of the GI tract to maximize drug reaching its absorption site in the solution state and, hence, ready for absorption. HBS is prepared by incorporating a high level (20–75 w/w%) of one or more gel-forming hydrocolloids (*e.g.*, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl

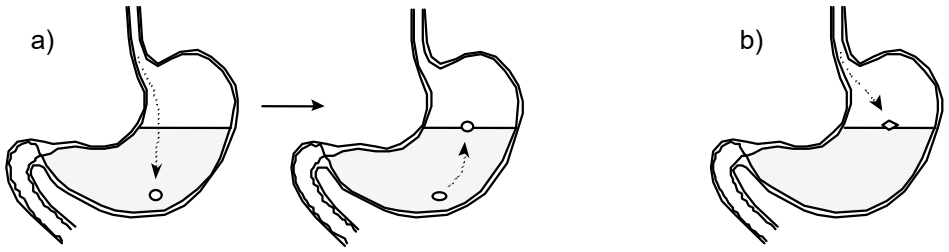


Figure 10.3 Devices with densities lower than 1 can be used to make systems floating in the stomach. The density of a device can be lowered after administration to the stomach (a) or can be made of lower density materials from the beginning (b).

methylcellulose, and sodium carboxymethyl cellulose) into the formulation and then compressing the granules into a tablet (or encapsulating into capsules).

On contact with gastric juice, the hydrocolloid in the device starts to absorb water and form a gelatinous barrier around the surface. The thickness of the gel barrier, which controls the drug release, increases with time. The density of the device becomes less than 1 and the device becomes buoyant in the gastric fluid for up to 6 h.

The Valrelease® tablet (Roche) is prepared by a simple pharmaceutical granulation process of homogeneous dispersion of valium, a tranquilizer, in hydrocolloid and pharmaceutical excipients. The granules are then compressed to form a compressed tablet. After oral intake, the hydrocolloid in the tablet absorbs gastric fluid and forms a colloidal gel that starts from the tablet surface and grows inward (Figure 10.4). The release of valium molecules is then controlled by matrix diffusion through this gel barrier. The Valrelease® tablet remains buoyant in the stomach as a result of the density difference between the gastric fluid ($d > 1$) and the gelling tablet ($d < 1$).

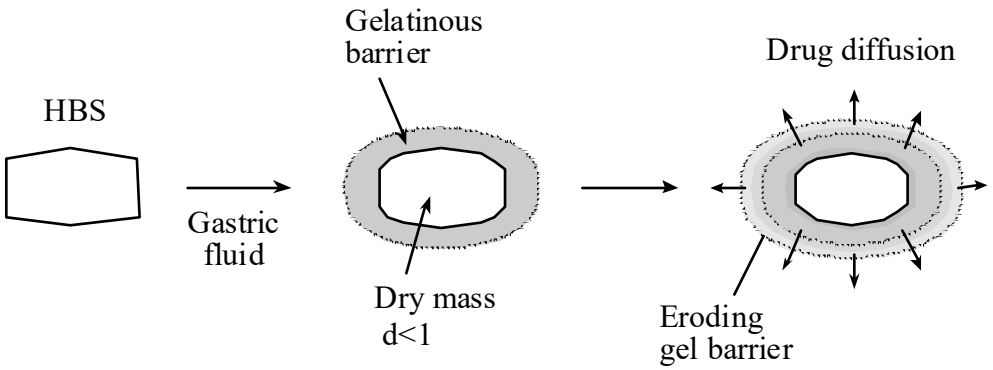


Figure 10.4 Description of the hydrodynamically balanced system (HBS). Diffusion of the gastric fluid to a dried HBS system results in a formation of the gelatinous polymer layer. Drug is release by diffusion and erosion of the gel barrier.

b. Gas-Generating Floating Systems

If an oral dosage form is loaded with HCO_3^- ions, it will produce carbon dioxide upon contact with acid in the stomach. The generated carbon dioxide can be trapped inside the beads. This makes the density of the beads less than 1 and as a result they become floating on the top of the stomach contents (Figure 10.5).

c. Low-Density Core Systems

The apparent density of an oral dosage form can be made less than that of the gastric juice. This will result in floating on the gastric juice and as a result residence time in the stomach is expected to be increased. Pop-corn or pop-rice can be first coated with enteric-coating materials (such as cellu-lose acetate phthalate or copolymer of acrylic acid and methacrylic

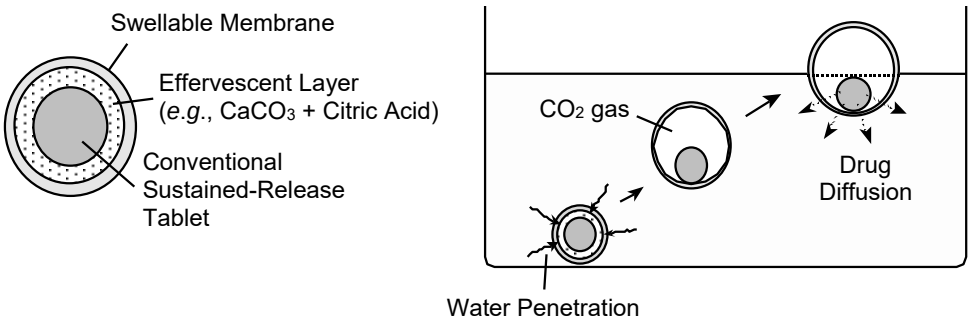


Figure 10.5 Structural characteristics (left) and floating mechanism (right) of the gas-generating microballoon system. The right figure shows penetration of water into the microparticle and generation of CO2 to make the system to float.

acid). This in turn can be coated with drug–polymer matrix or polymer mem-branes for controlled-release of drugs. These types of oral dosage forms are also called intragastric-floating drug-delivery systems.

Note: Intragastric floating devices may work as long as there is enough gastric juice in the stomach. Since stomach fluids are emptied in less than 30 min, floating devices require a constant intake of water. This defeats the whole purpose of taking controlled-release dosage forms.

d. Low-Density Mucoadhesive Microparticles

The mucoadhesive property can be added to the low-density devices (see Figure 10.6), but mucoadhesives usually do not work well owing to the fouling of the surface by the variety of components present in the stomach.

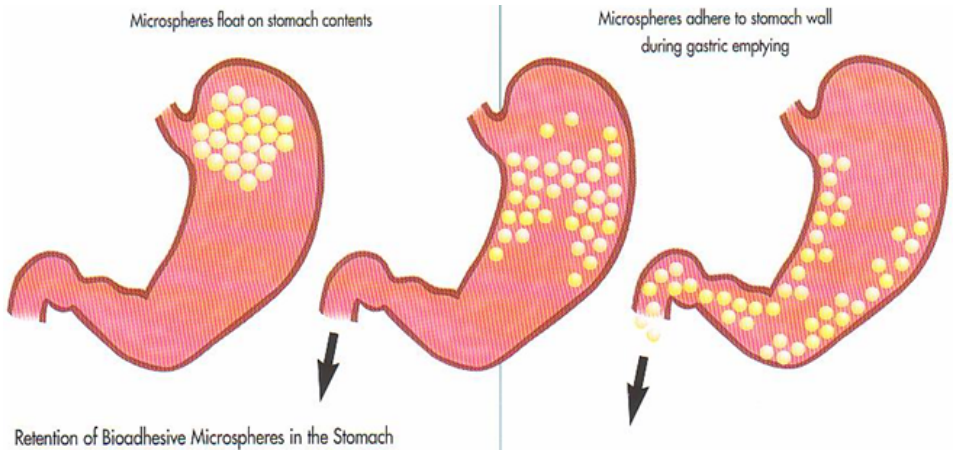


Figure 10.6 Attachment of a mucoadhesive dosage form to the mucus layer in the stomach.

2. High-Density Oral Dosage Forms

It was suggested that the increase in the density of the oral dosage forms from 1.0 to 1.6 can increase the average GI transit time. The density of the oral dosage form can be increased by coating the drug layer around an

inactive heavy core (*e.g.*, barium sulfate, zinc oxide, magnesium hydroxide, or iron powder). The heavy materials may be mixed with drugs to form a reservoir for diffusion-controlled reservoir systems. Many studies show that the high-density formulations have very little effect in extending the gastric residence time.

3. Mucoadhesives on Oral Dosage Forms

If oral controlled-release dosage forms are coated with mucoadhesive polymers that are adhesive to the mucus layer covering the gastric tissue (Figure 10.6), its gastric retention time will be increased dramatically. The best mucoadhesive known today is poly(acrylic acid). The problem with mucoadhesive approach is that the current mucoadhesives are nonspecific to mucins. In other words, mucoadhesives adhere to almost anything and for this reason it is difficult to use it in the oral drug delivery. If a method to protect the mucoadhesive until it interacts with mucus layer is developed, this approach will be useful not only in the extension of the gastric retention times but also targeting to a specific region in the GI tract.

4. Unfoldable, Extendible, or Expandable Systems

a. Systems unfolding in the stomach

This type of device comprises one or more retention arms that are noncontinuous compressible elements. The retention arms are initially folded to make the whole system smaller (Figure 10.7). Since the device has to be emptied after all the drug is released, it is important to connect the compressible retention arm to the drug delivery module using a biodegradable polymers.

b. Systems extending to complex geometric shapes

Studies have shown that devices that extend in the stomach to certain geometric shapes can prolong gastric retention time. The geometric shapes include a continuous solid stick, a ring, and a planar membrane. Since these devices should be small in the beginning for easy swallowing, they have to be compressible to a small size and expandable to a size large enough to prevent emptying through the pylorus. The longest length of the final dimension of devices varied from 2 cm to 5 cm while the shortest

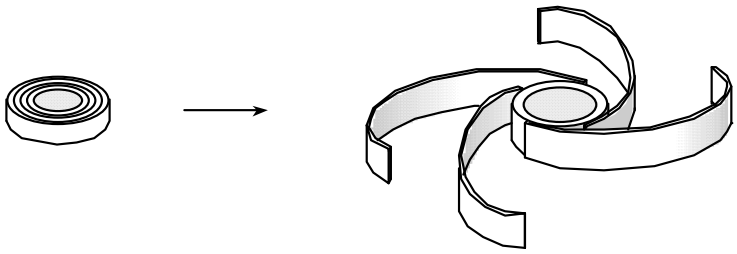


Figure 10.7 The system with the coiled arms (left) can unfold the arms (right) in the stomach. The expanded form is expected to resist gastric retention.

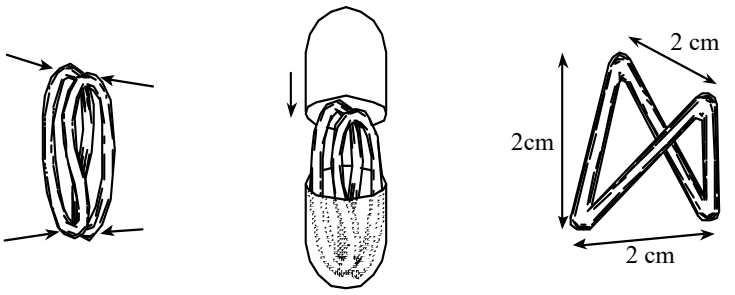


Figure 10.8 The tetrahedral form of the device is compressed (arrows in the left figure) for encapsulation (center). In the stomach, the preferred tetrahedral form (right) is restored for extended gastric retention.

length was around 2 cm. Figure 10.8 shows an example of this type of approach. In beagle dogs, some of these devices showed extended gastric residence time (longer than 24 h) in the fasted condition. In humans and larger dogs, however, the devices emptied from the stomach much faster.

c. Systems expanding to larger sizes

i. Concept

The idea here is to make devices that are small enough for easy swallowing but expandable upon contact with gastric juice to a size sufficient to cause retention of the device in the stomach (*i.e.*, a size too large to pass through the pylorus). The expandable device can swell either by absorbing water from the gastric juice or by evaporation of solidified or liquefied gas present in the device. The concept is shown in Figure 10.9. This type of device is made to a size slightly larger than the diameter of the pyloric canal (about 1 cm to 4 cm; usually 2 cm in humans), until completion of the prescribed therapeutic regimen. Because the systems have to be removed from the stomach eventually, they have to be made either degradable or deflatable. Figure 10.10 shows an example of this type of approach. As shown in the figure, the extent of swelling is rather modest. The expanded device will be deflated upon removal of the plug by biodegradation.

5. Superporous Biodegradable Hydrogel Systems

This approach is based on the swelling of unique hydrogel systems. The

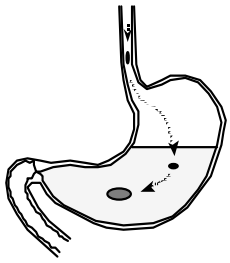


Figure 10.9 A device expanding moderately in the stomach

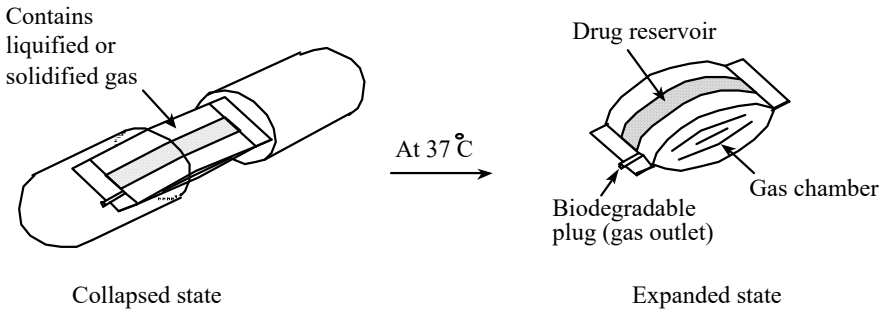


Figure 10.10 An example of expandable device based on gas evaporation.

principal difference from the devices described earlier on expanding systems is that the extent of swelling of superporous hydrogels is far beyond than that obtainable by other means. The swelling ratio (volume of the swollen gel/volume of the dried form) can be easily over 1,000 compared to only 2–50 of expanding systems. The superporous hydrogels, with their superswelling property, possess properties that no other devices have.

The main concept here is to utilize the superswelling properties of superporous hydrogels to extend gastric retention time. The superporous hydrogels can also be made biodegradable (*e.g.*, degradable by pepsin in the stomach). Thus, as shown in Figure 10.11, the dried superporous hydrogel formulation in an ordinary capsule, which can be easily swallowed, swells to a size up to several centimeters, which is too large to be emptied from the stomach. As drug is released or after all of the drug is released, the superswollen hydrogel degrades and eventually empties from the stomach. As mentioned above, the swelling ratio of superporous hydrogels is in the range of several hundred at a minimum and can be much higher than 1,000. This means that each dimension can be increased 10 times.

E. COLON-SPECIFIC DELIVERY SYSTEMS

CODES™ is a colon-targeted delivery system (from Yamanouchi Shaklee Pharma) enabling targeted release of proteins/peptides and other drug

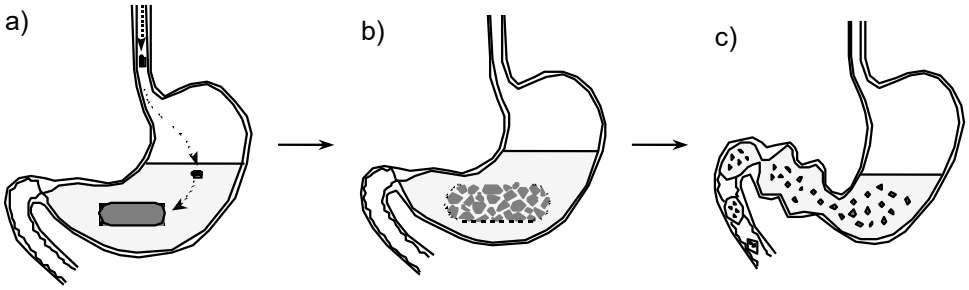


Figure 10.11 A dried superporous hydrogel swells to a huge size in the stomach (a). As the drug is released, the swollen hydrogel can undergo degradation (b) and eventually emptied from the stomach (c).

compounds in the colon. Lactulose, which is degraded when exposed to the colon's microflora, is included in the drug core formulation, and this allows drug release in the colon subsequent to the formation of organic acids. The drug core is prevented from degradation/absorption prior to the colon by first an enteric coating and then a cationic polymer coating for passage through the small intestine to the cecum. pH changes in the large intestine trigger erosion of the cationic polymer, and lactulose diffuses through the cationic polymer and is degraded by cecal microflora. Organic acids produced by the microflora dissolve the cationic polymer, permitting drug release.

CODES™ is a new drug delivery technology enabling targeted release of proteins/peptides and other drug compounds in the colon, an area where drug release is difficult to achieve. By including lactulose (which is degraded when exposed to the colon's microflora) in the drug core formulation, drug is released in the colon subsequent to the formation of organic acids. The drug core is prevented from degradation/absorption prior to the colon by first an enteric coating and then a cationic polymer coating for passage through the small intestine to the cecum.

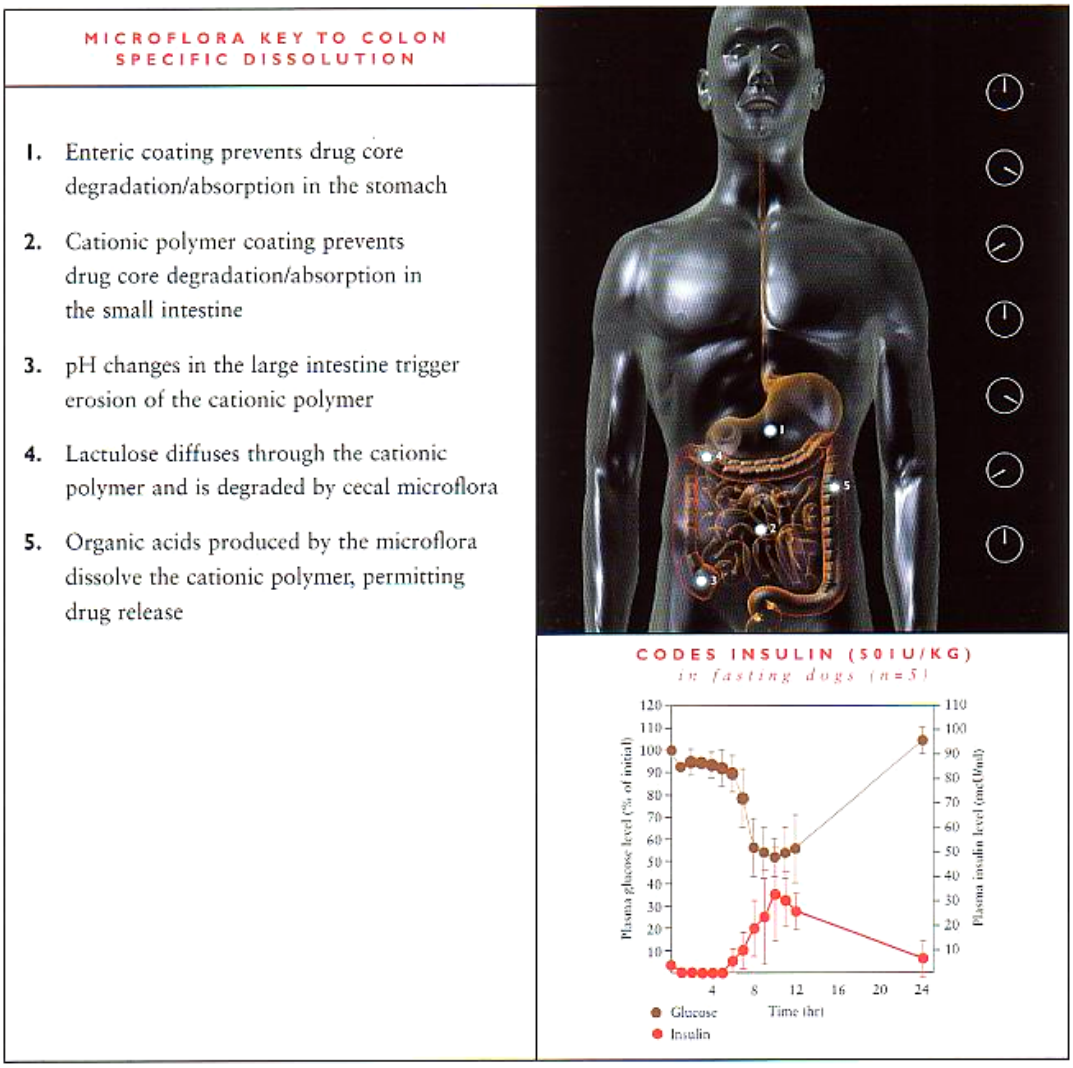


Figure 10.12 CODEs™ system from Yamanouchi Shaklee Pharma.

Oral Controlled-Absorption System (OCAS™ from Yamanouchi Shaklee Pharma) is a drug delivery technology enabling the gradual release of drug active as the tablet system travels throughout the digestive tract, including the colon, an area where the drug release is difficult to achieve. The hydrophilic gel-forming polymer matrix tablets of OCAS™ prevents degradation of drug prior to intestinal delivery. It also allows the formulation of single daily doses and ensures stable action by minimizing the effects of individual differences and food consumption on drug absorption.

The InteliSite® capsule (Innovative Devices LLC) is 10 mm in diameter and 35 mm in length (see Figure 10.13). Two versions of the InteliSite® capsule are available. One version delivers solutions or suspensions; another version delivers powder formulations.

The InteliSite® capsule is loaded with a drug solution or powder formulation in a specially designed reservoir. When the capsule reaches the desired location in the gastrointestinal tract it is externally activated by remote control. Activation is accomplished by exposing the capsule to a radiofrequency magnetic field that induces a small amount of heat in the capsule's activation assembly. This causes two shape-memory alloy wires to straighten, rotating an inner sleeve of the capsule in relation to an outer sleeve. The rotation process aligns a series of slots in the sleeve surfaces permitting the contents to be released into the specific area of the GI tract. After activation, the InteliSite® capsule passes harmlessly through the body.

After the InteliSite® capsule is loaded with either the liquid or powder

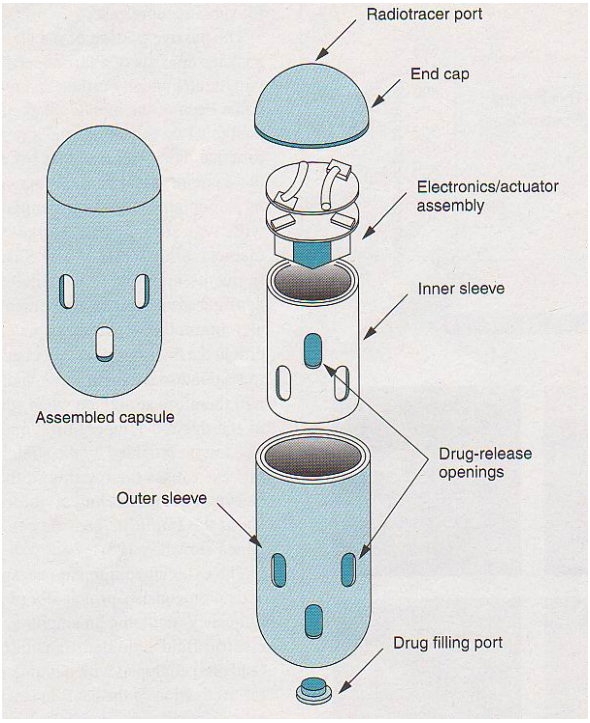


Figure 10.13 Drug delivery to specific sites in the GI tract using the InteliSite® delivery system.

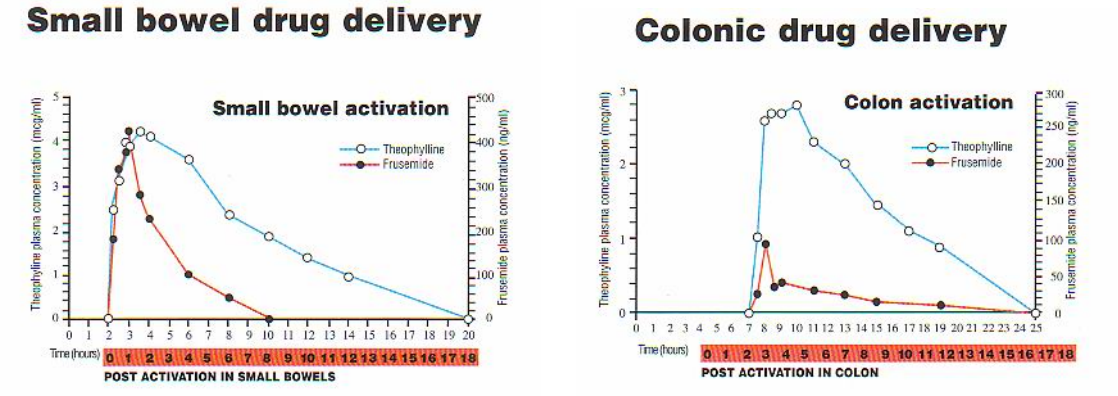


Figure 10.14 Concentrations of theophylline and frusemide after releasing the drugs from an InteliSite® capsule.

formulation, it is administered orally. The capsule is tracked through the GI tract using γ-scintigraphy. Either Indium (^{111}In) or Technetium (^{99m}Tc) gamma isotopes may be incorporated into the capsule for tracking purposes. The capsule and release of drug can be tracked simultaneously using gamma cameras with dual isotope detection capabilities.

F. SWALLOWABLE VIDEO PILLS

The capsule-size video camera was developed to image the digestive tract for 24 h after swallowing (see Figure 10.15). Figure 10.16 shows the relative size of the device from Given Imaging Co. (Yoqneam, Israel) who made the 11 × 30-mm capsule with a video-imaging capability (Powell,

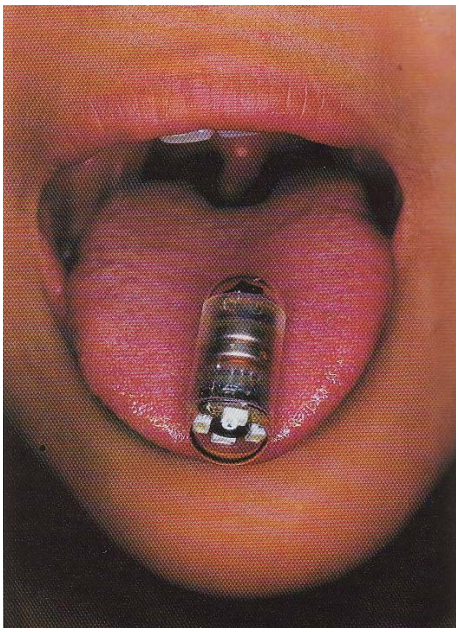


Figure 10.15 Swallowing a not so bitter pill (Carmichael *et al*., 2001).

Figure 10.16 Video camera in a capsule (Powell, 2000).

2000). The images are relayed by radio to a Walkman-like receiver at-

Figure 10.17 Schematic of the M2A® endoscope capsule from Given Imaging (http://www.borland-groover.com/capsule_endosocpy.htm) [*sic*].

tached to the patient's belt at the rate of two still-images per second. All of the images can be downloaded later to assemble a video that gives a more accurate and revealing picture of what's going on in the intestine than any image obtained by endoscopy. More than 8 million endoscopy procedures are performed yearly, in which patients have to be sedated for fiber-optic cables to snake through the intestine. In addition to its uncomfortably invasive procedure, endoscopy method cannot reach two thirds of the small intestine. The pill camera (see Figure 10.17) goes down easily with a sip of water. This type of device can be developed further to administer medication, perform biopsies, and diagnose illnesses (D'Agrese, 2001).

G. SINGLE UNIT VERSUS MULTIPLE UNITS ORAL DOSAGE FORMS

1. Single-Unit Dosage Forms

Oral controlled release dosage forms are available either as a large, single-unit system or as encapsulated multiple-unit system. The drug release from a single-unit system depends on a single drug release mechanism. In

the absence of proper platforms, gastric retention time of single unit oral dosage forms is extremely variable. This leads to a difficulty in customizing release rates to match regional release and absorption characteristics within the GI tract.

2. Multiple-Unit Dosage Forms

Multiple-unit oral dosage forms tend to provide more predictable gastric-emptying time. Multiple pellets or granules are rapidly dispersed throughout the stomach and small intestine, and show much longer and much more reproducible, median transit times compared with single-unit dosage forms. For example, when a 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.

The incidence of upper GI tract bleeding of the two KCl products, microencapsulated formulation (Micro-K® Extencaps) and wax-matrix preparation (Slow-K®), was compared. The study confirmed the previous suggestions that microencapsulated formulations of KCl are associated with a lower risk of upper GI tract bleeding than wax-matrix formulations (Strom *et al*., 1987). The dispersibility of the microcapsules and the controlled release of ions tend to minimize the likelihood of high localized concentrations of KCl and resultant mucosal ulceration within the GI tract.

Naprelan® is a once-daily long-acting formulation containing nonsteroidal antiinflammatory drug (naproxen) for the treatment of arthritis and pain. Naprelan® was developed by Elan Corp., Inc., and is marketed

Figure 10.18 Examples of multiple-component capsules.

by Wyeth-Ayerst Laboratories. Naprelan® offers a unique combination of

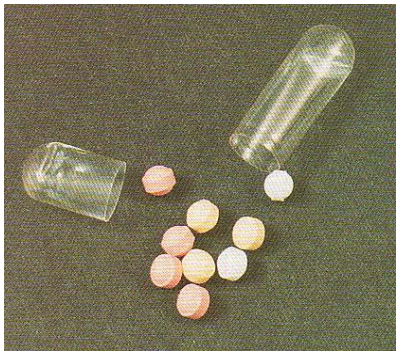


Figure 10.19 The PRODAS® multi-unit controlled-release system.

rapid onset of pain relief, a sustained-release mechanism allowing for once-daily dosing through Elan's IPDAS® technology. The Intestinal Protective Drug Absorption System® (IPDAS®) is a multiparticulate tablet technology that can be used to enhance the GI tolerability of potentially irritant or ulcerogenic drugs such as non-steroidal antiinflammatory drugs. The multi-particulate nature of the IPDAS® formulation ensures wide dispersion of irritant drug through the GI tract. The IPDAS® is composed of numerous high-density controlled-release beads. Beads of drug-polymer micromatrices are coated with polymer membranes that form a rate-limiting membrane *in vivo* for diffusion controlled release.

3. Multi-Unit Dosage Forms

To include advantages of both single-unit and multiple-unit systems, an alternative multi-unit controlled-release system, known as PRODAS® (Elan Pharmaceutical Technologies, Athlone, Ireland), was developed. It combines the advantages of tablet-based technology with presentation as a multiunit system (Butler *et al*., 1998). A number of small (3–4 mm) tablet units are filled into a capsule.

H. Oral Delivery of Peptides and Proteins

In spite of these major efforts in developing effective oral formulations for peptide and protein drug candidates for the past several decades, relatively little progress has been made in preparing the safe and effective oral formulations for peptides and proteins. The main hurdles are listed in Table 10.3.

Table 10.3 Hurdles in the Development of Oral Delivery of Peptide and Protein Drugs

Poor intrinsic permeability of peptides and proteins across biological membranes owing to their hydrophilic nature and large molecular size
Susceptibility to enzymatic attack by intestinal proteases and peptidases
Rapid post-absorptive clearance
Chemical instability, including tendencies to aggregate and nonspecific adsorption to a variety of physical and biological surfaces

Formulation of peptide and protein formulations should address all of the above issues simultaneously. Novel drug delivery systems that can overcome the problems of lack of oral activity will be crucial in converting the intravenously active compounds to ones with a facilitated means of delivery (Somberg, 1996). It would be ideal if one could synthesize small molecules that act like the protein molecules. Even so, the end products would still be peptides which may not be orally active. However, the delivery of peptides would be substantially easier than the delivery of whole proteins.

1. Overcoming poor intrinsic permeability using absorption enhancers

The basic barrier properties of the intestinal epithelial cell membrane against peptides and proteins can be modified by using permeation enhancers, such as salicylates, mixed bile salt-fatty acid micelles, chelators, fatty acids, acylcarnitines, surfactants, and medium chain glycerides. In all cases, however, bioavailability was still fairly low and variable (< 10% in general). If the permeation enhancers are able to increase the permeability of peptides and proteins to much higher level, it means that anything present in the GI tract can be absorbed as well. This is very dangerous.

2. Protection from enzymatic degradation

Peptides and protein drugs may be protected from enzymatic degradation using protease inhibitors, such as sodium glycocholate, camostat mesilate, and bacitracin. Addition of protease inhibitors to insulin increased the glucose-lowering activity of insulin administered to rat small intestine and colon. The processes involved in peptide absorption (*i.e.*, delivery or peptide release, absorption, proteolytic attack) are all inter-related and depend on the kinetics of each individual process. It is not clear whether simultaneous release of protease inhibitors along with a given peptide is the optimal pattern.

A few amino acid residues of peptides and protein drugs may be altered to prevent enzymatic degradation. This approach may work fine, but it results in peptides and proteins that may or may not maintain bioactivity. Furthermore, altered peptide and protein drugs are essentially new drugs, and therefore should undergo FDA approval process all over again as new drugs.

3. Chemical stability and aggregation

Peptides and proteins often possess physical properties that present significant formulation problems not encountered with many small, organic drug molecules. Because of the complex nature of peptides, self-aggregation is always a concern in formulation efforts. The tendency of insulin to form hexamers is well documented and the absorption of hexamers will most likely be very different than monomer absorption. The use of various surfactant approaches to maximize monomer concentration during peptide release may afford advantages in minimizing the size of the complex which must cross epithelial cell layers.

It is important to understand the problems associated with the development of oral controlled release dosage forms for peptide and protein drugs. The answers can be found only if the problems are clearly defined.

Recently, a number of new oral delivery systems were claimed to deliver macromolecular drugs (such as insulin, growth factors, or heparin) through the GI tract. Emisphere Technologies, Inc., showed that Emispheres® can deliver macromolecules (mainly heparin) by oral administration. Emispheres® are made of novel, peptide-like delivery agents (*e.g.*, sodium *N*-(2-hydroxybenzoyl)aminocaprylate)

II. BUCCAL CONTROLLED-RELEASE DOSAGE FORMS

A. VARIOUS BUCCAL DOSAGE FORMS

Buccal delivery allows faster onset of drug action and is highly useful for a short duration ranging from a few minutes to several hours. The main advantage of buccal delivery is the barrier property by buccal membrane is much reduced compared with the skin. In addition, buccal delivery can avoid extensive pre-systemic clearance occurring for some drugs after oral administration. Thus, many conventional buccal dosage forms (*e.g.*, tablets, troches, or lozenges) have been developed for nitroglycerin, ergotamine, nicotine, buprenorphine, methyl testosterone, and nifedipine.

1. Periodontal Implants

Periodontal disease is an infection of the gums and the chronic inflammation of the gums destroys the soft tissue and bone that supports the tissue. The inflammation in the periodontal pockets is the number one cause of tooth loss. Recently, diverse controlled release buccal dosage forms have been developed.

a. Actisite® periodontal fiber

Actisite® periodontal fiber (Alza Corp.) is made of a 23-cm monofilament of EVA copolymer (0.5 mm in diameter) that can be placed in periodontal pockets to release tetracycline hydrochloride for 10 d. It contains 12.7 mg of evenly dispersed tetracycline hydrochloride. Another example is the mucoadhesive buccal patch for the delivery of buprenorphine. Oral administration of buprenorphine results in low bioavailability owing to extensive pre-systemic biotransformation. Buprenorphine is commercially available as an injectable in the U.S. A mucoadhesive buprenorphine buccal patch is in development by 3M (McQuinn *et al*., 1995). Buprenorphine, which is currently used in the treatment of both acute and chronic pain, is also being investigated as a potential treatment for opiate dependence since it is an opiate with mixed agonist-antagonist properties. A simple buccal delivery of buprenorphine may be very useful in the treatment of pain as well as opiate dependence.

b. Atridox

Atrigel® (Atrix Laboratories, Inc.) is a liquid polymer system that solidifies upon injection into the body to provide a matrix for delivery of the drug. Biodegradable polymers, such as polyglycolide, polylactide, polycaprolactone, and copolymer thereof, are dissolved in biocompatible solvents (*e.g.*, *N*-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, and acetone). Atridox® contains 8.5% doxycycline and was approved by the FDA in April, 1998. The Atrigel® system consists of two biodegradable polymers, poly(lactic acid) and polycaprolactone, dissolved in 2-pyrrolidone, *N*-methyl-2-pyrrolidone, dimethyl sulfoxide, or acetone. When the liquid product is injected into the periodontal pocket, contact with tissue fluids results in precipitation of the polymer taking the shape of the periodontal pocket. The included doxycycline is released over a seven-day period.

2. Buccal Patches

The buccal patch in development by 3M is made as follows. A buprenorphine free base (8% w/w), Carbopol® 934 (52%), polyisobutylene (35%), and polyisoprene (5%) were first homogeneously mixed by a two-roll mill and then the mixture was compressed to the appropriate thickness (~0.6 mm thick). A membrane backing made of ethylcellulose was then applied to one side of the compressed material and then circular disks (0.5 cm^2) were punched from the material. Each soft, flexible disk contains 2.9 mg of buprenorphine. The ethylcellulose backing is to retard drug release from one side of the disk and to prohibit adhesion to opposing side tissues. In this formulation, Carbopol® 934 functions as an adhesive to the buccal mucous membrane.

DentiPatch® (lidocaine transoral delivery system) is used for the prevention of pain of oral injections and soft-tissue dental procedures. It was developed by Noven Pharmaceuticals Inc. The system is about the size of a small paper clip and is applied directly onto the gums. The product numbs the area of the mouth covered by the patch in about two minutes and remains effective for up to 45 min.

A transoral patch is used as a delivery system for protein and peptide drugs of large molecular size, such as insulin by Noven Pharmaceuticals Inc. In a proof of concept study, patches containing insulin placed in the mouth of non-diabetic subjects was claimed to produce a pharmacological effect equivalent to a small dose of injected insulin. Transoral delivery of drugs from patches could offer a few advantages that might translate into improved efficacy and patient compliance with certain drugs.

3. Gums

Nicorette® gum was first made available as a prescription product in 1984 (nicotine polacrilex) and over the counter in February 1996. The gum is chewed until a sensation, indicative of nicotine release, is felt in one's mouth. The Nicorette® gum is then placed back between the cheek and gum for absorption of nicotine through the lining of the mouth.

4. Inhaler

Nicotrol® Inhaler (nicotine inhalation system) was approved by FDA in May, 1997. This product is only available by prescription. Patients hold the Nicotrol® Inhaler between fingers and draw in air. Nicotine is delivered in a way that can help ease withdrawal symptoms while quitting without harmful tars, carbon monoxide, and smoke of a cigarette. Nicotine never reaches the lungs of the individual user. Instead, it is absorbed through the mucous membranes in the mouth and throat. Side effects are local irritation in throat and mouth, and coughing.

B. FAST-DISSOLVING TABLETS

In some cases, buccal delivery is used for quick delivery of drugs. Sometimes it is preferred to make oral dosage forms to dissolve (or disperse) fast so that drugs can be absorbed as fast as possible. Also, it is preferred to take oral medication without water and without swallowing. This property is especially important and critical for drug delivery to the geriatric and pediatric patients. For this reason, oral dosage forms which dissolve fast in the mouth without water have been developed.

1. Zydis® System

RP Scherer Corp. developed the Zydis® drug delivery system, which is a freeze-dried, porous wafer system containing the drug substance that dissolves in seconds when it comes in contact with saliva on the tongue. The property of instant dissolving on the tongue may be useful when patients have difficulty of swallowing (such as in Parkinson's disease, nausea, and dyspepsia) or when water is not readily available. The fast dissolving technology is important for improving patient compliance, especially for pediatric and geriatric patients, and for improving treatment.

Several Zydis® formulations have been launched in Europe and in America: Pepdine® (Pepcid® formulation by Merck & Co.); Imodium® Lingual (Janssen Pharmaceutica Inc.); Feldene Melt®, Feldene Fast® and Feldene Flash® (non-steroidal antiarthritic products from Pfizer Inc,); Claritin RediTabs® (Schering Corp.); and Dimetapp® Quick Dissolve Tablets (AH Robbins). A Zydis® formulation for the antiemetic product Zofran® is planned by GlaxoWellcome for those patients who may have trouble swallowing traditional tablets and capsules. The original formulation and process patent for the Zydis® system will expire in 2002. In the production of Zydis® products, a solution or suspension of drug is first dosed into preformed blisters. The blisters of products are then rapidly frozen by passing through a freeze-tunnel. Finally the frozen product is lyophilized (see Figure 10.20).

2. WOWTAB® Quick-Dissolve Tablet

WOWTAB® Quick-Dissolve Tablet Technology from Yamanouchi Shaklee Pharma (see Figure 10.21). It employs without-water (WOW) quick-dissolve tablet technology that can be manufactured by the conventional tablet machines. Thus, it is much easier to make with a lower cost

than Zydis® system. The presence of specific excipients results in immediate dispersion of the tablet once placed in the mouth. In about 20 s, it is totally dispersed in the mouth.

Kidmed™ acetaminophen melting tablets (Perrigo: Allegan, MI 49010). Inactive ingredients: aspartame, colloidal silicone dioxide, crospovidone, magnesium stearate, mannitol, methacrylic acid copolymer, polyacrylate dispersion, stearic acid.

Figure 10.20 The Zydis® process.

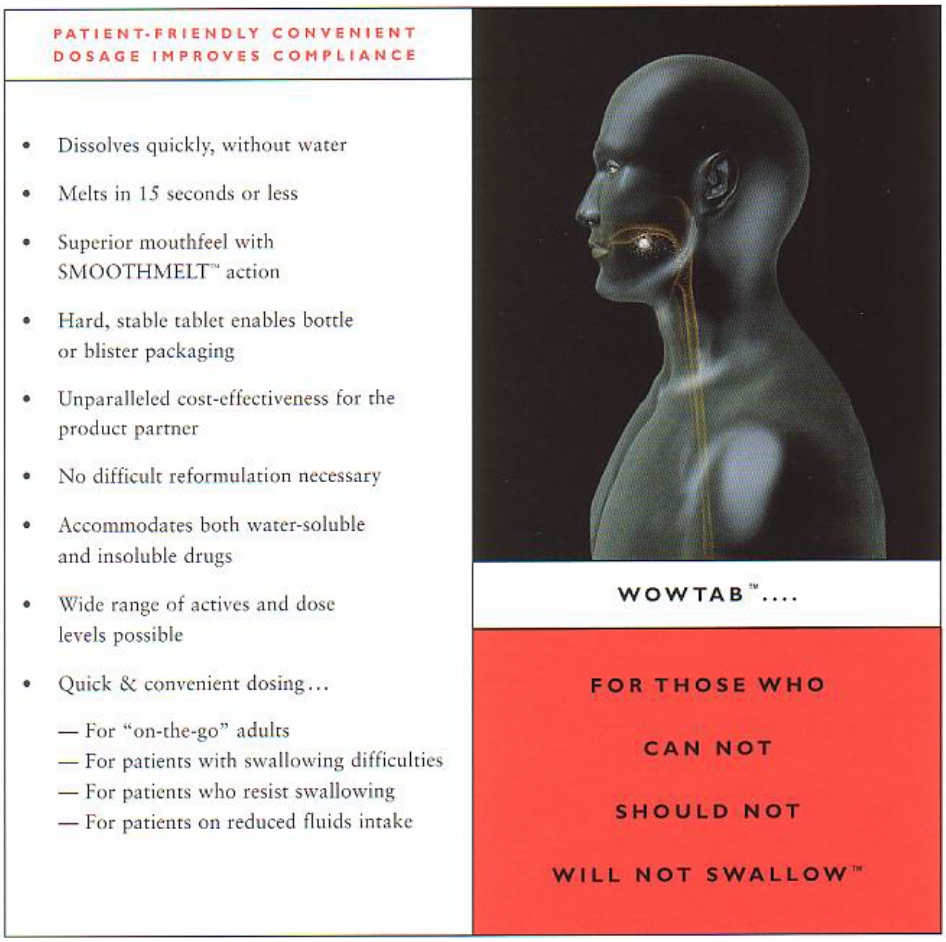


Figure 10.21 WOWTAB® technology from Yamanouchi Shaklee Pharma.

The Flashtab® technology is used to improve the ease of administration and palatability of difficult-to-swallow and bad-tasting medicines. The technology combines two key proprietary technologies: fast melting and taste-masking. Flashtab® tablets consist of microparticles that disperse quickly in the mouth thereby allowing the rapid and safe release of the active ingredients into the organism. They can be administered anywhere, without the need for water or chewing.

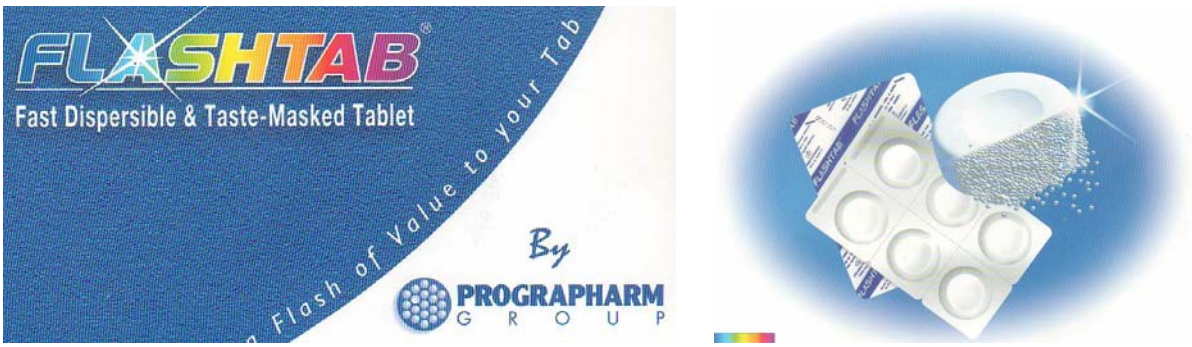


Figure 10.22 Flashtabs® (Prographarm Group: Paris, France) contains taste-masked microspheres.

3. Solblet®

SOLBLET® tablets disintegrate rapidly with saliva in the mouth or when taken with water (see Figure 10.23). They are easy to swallow, making them especially agreeable to patients with throat-related problems. The unique SOLBLET technology has been developed independently by Kyowa Hakko, Japan. The manufacturing of a SOLBLET® tablet starts with blending the active pharmaceutical ingredient with sugar and wet granulating the mixture with ethanol and water. The wet mass is then dried and compressed into tablets. The material is formulated to allow much more rapid absorption of water into tablets when compared to conventional tablets.

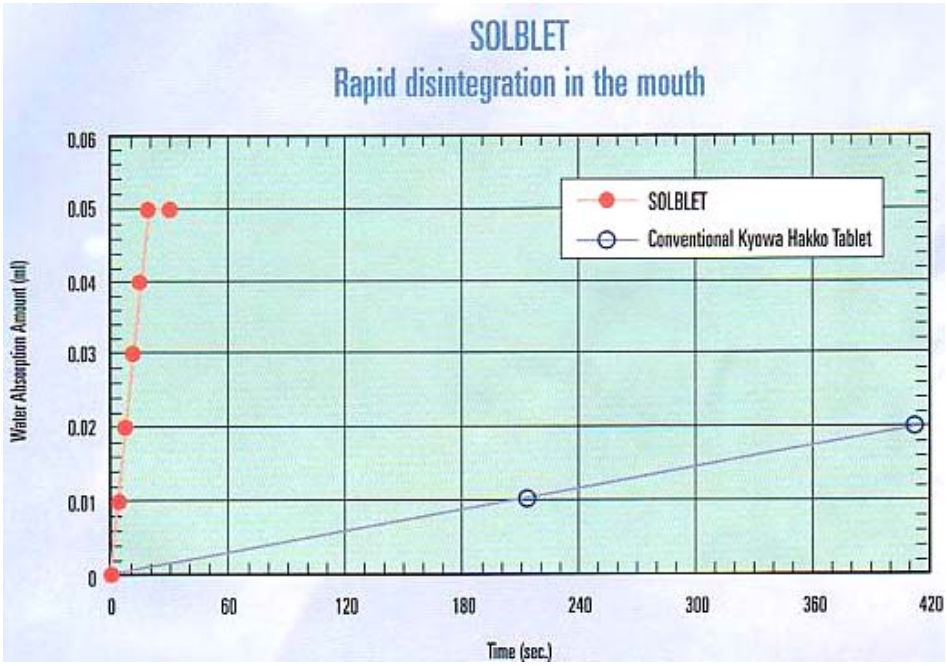


Figure 10.23 Water absorption rate of SOLBLET® tablets.

4. SolTab™

Remeron® SolTab™ from Organon is an orally disintegrating tablet that has been approved for the treatment of depression. Unlike other antidepressant tablets, which must be swallowed whole, Remeron SolTab® dissolves on the tongue within 30 s. This easy delivery method may enhance patient compliance as the tablet can be swallowed with or without water, chewed or allowed to disintegrate. Along with its unique delivery system, Remeron® SolTab™ has a novel pharmacological profile that increases the levels of both norepinephrine and serotonin in the brain to effectively fight depression. This is in contrast to many antidepressants, which only increase serotonin. According to the company, the product is suitable for depressed patients of all ages.

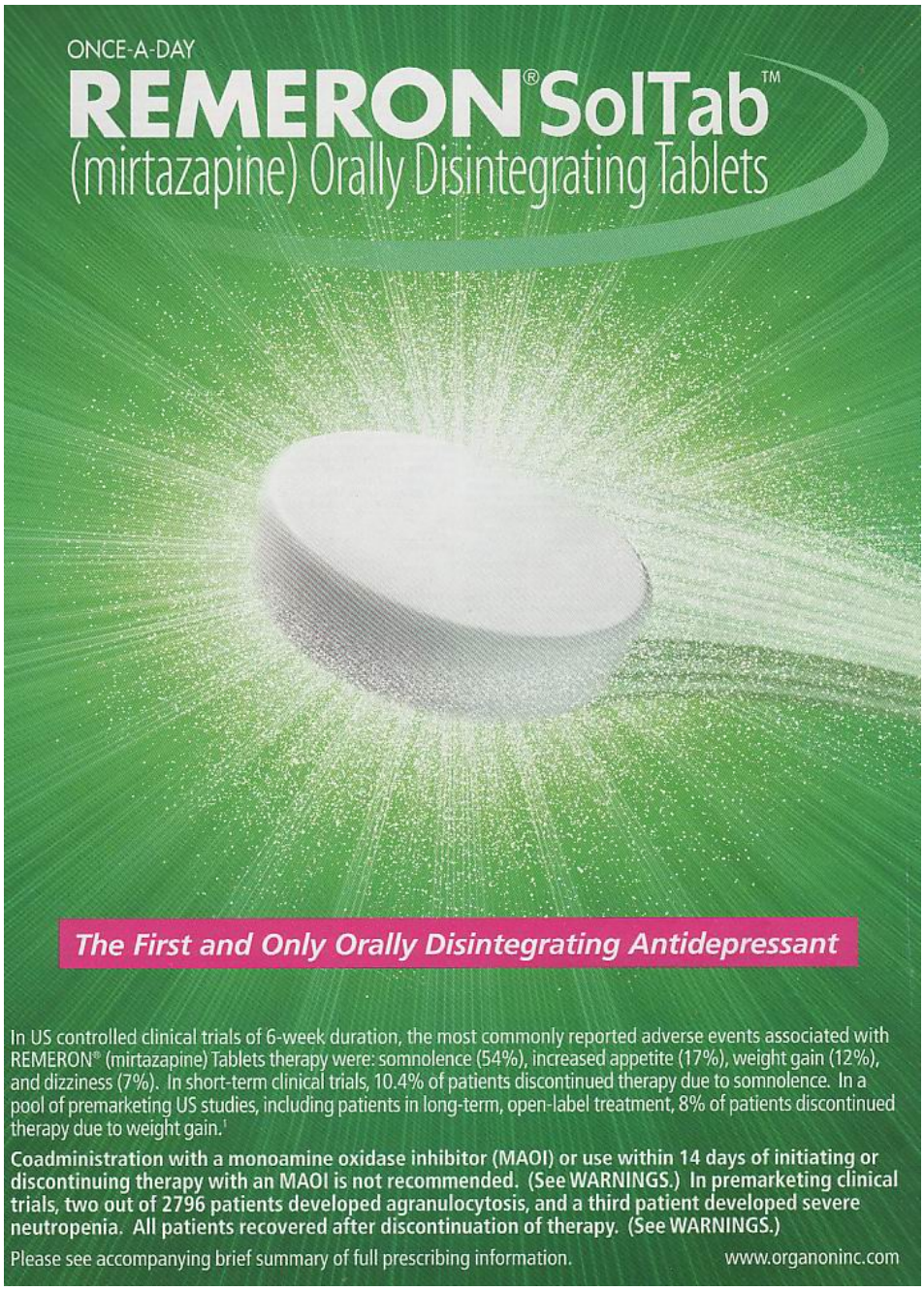


Figure 10.24 Advertisement for Remeron® SolTabs™.

5. Cima's Quicklets®

Cima Labs also produced OraVescent™ system (see Figiure 10.25). OraVescent™ uses effervescence and pH control to enhance delivery of drugs through the mucosa of the oral cavity. In clinical studies, fentanyl absorption from OraVescent™ was shown to be faster and higher than it was from a marketed fentanyl transmucosal delivery system (Actiq®). This is not surprising since the onset of action from the transdermal system is usually very low. The real control experiment should have been regular tablet formulation.

Figure 10.25 Available products utilizing the Quicklets® technology.

6. CEFORM™ Microsphere technology

Shearform™ technology is used for making quick dissolve dosage forms. A dry blend of saccharides and polysacchaides is subjected to a combination of centrifugal force and controlled temperature to produce amorphous cotton candy-like fibers known as "floss." A controlled crystallization of the floss creates polycrystallite structures with very high specific surface areas and corresponding rapid dissolution. This is used to make Fuisz's quick-dissove FlashDose® technology.

C. Supersonic Powder Injection System

Recently, supersonic powder injection was developed for drug delivery through the buccal mucosa and other mucosal surfaces. Upon actuation of the device, the expanding helium gas bursts a membrane that results in a shock wave traveling at supersonic speeds down a shock tube. Upon impact with the inverting dome, the rapid inversion of the dome results in acceleration of the drug particles and subsequent penetration of mucosal tissue. Delivery of testosterone to the buccal surface by transmucosal powder injection in beagle dogs resulted in very rapid absorption owing to the high level of vascularization of the buccal mucosa. The observed bioavailability is 19% relative to subcutaneous injection.

D. Limitations of Buccal Delivery

There are limitations and disadvantages in buccal drug delivery as listed in Table 10.4.

Table 10.4 Limitations and Disadvantages in Buccal Drug Delivery

Limited surface area for absorption
Concerns on taste and comfort in a highly innervated area
Difficulties of adhesion to a mucosal surface for extended periods without the danger of swallowing or chocking on a device
Potential bacterial growth
Blockage of salivary glands associated with prolonged occlusion

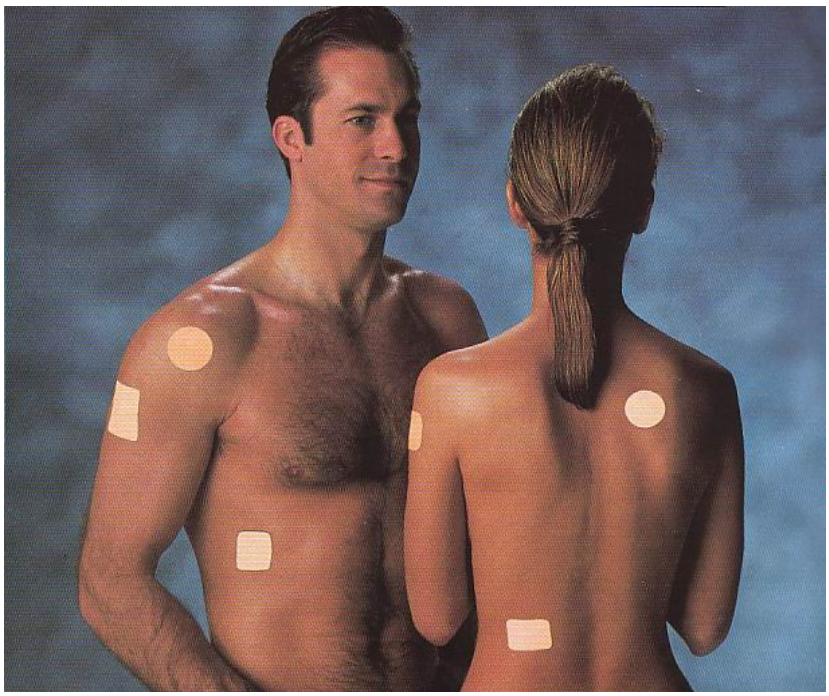


Figure 10.26 Examples of transdermal controlled-release patches.

III. TRANSDERMAL CONTROLLED-RELEASE DOSAGE FORMS

A large number of systemically-active transdermally-delivered drugs have been developed and approved for the last few decades. Although there is no question that transdermal administration has been effective for many drugs, it is important to know that the delivery of drugs via the skin is subject to some substantial constraints, limiting its general applicability. Through the years, the public has accepted the "patch" treatment as a viable way of administering drugs.

A. IMPORTANCE OF TRANSDERMAL THERAPY

The transdermal route provides drug administration to the blood stream without first passage through the GI tract. For example, nitroglycerin has a 90% hepatic first-pass effect after oral administration, but no first-pass effect after transdermal delivery.

1. Transdermal delivery can results in not only local effect but also systemic effect.
2. No first-pass effect
3. Drugs avoid the pH swings in the GI tract that can cause variability in absorption.

B. LIMITATIONS TO TRANSDERMAL CONTROLLED RELEASE

If the transdermal drug delivery is so advantageous and widely accepted, then the question may arise as to why not all the drugs are administered transdermally? This is because of the following limitations.

1. Difficulty of Permeation through Human Skin

The most superficial and least permeable skin layer, the stratum corneum, provides a uniquely impressive resistance to molecular transport both from and into the body. From an evolutionary standpoint, the skin did not develop as an epithelium through which absorption was intended. Quite the reverse: the architecture and biology of the skin is, in large part, directed towards the construction of a highly efficient barrier to the outward loss of water. Since human skin is a highly effective physical and chemical barrier, and delivery of drugs through the human skin is rather difficult for most drugs. Daily dosages of about 5 mg are most preferred. Nicotine patches deliver more than 20 mg of nicotine per day.

2. Skin Irritation (or Contact Dermatitis)

One of the main problems is the irritation or sensitization of the skin. Excipients and absorption enhancers may increase percutaneous absorption. Chlorpheniramine delivered from cellulose triacetate membrane causes irritation. The irritation was substantially reduced by reacting chlor-

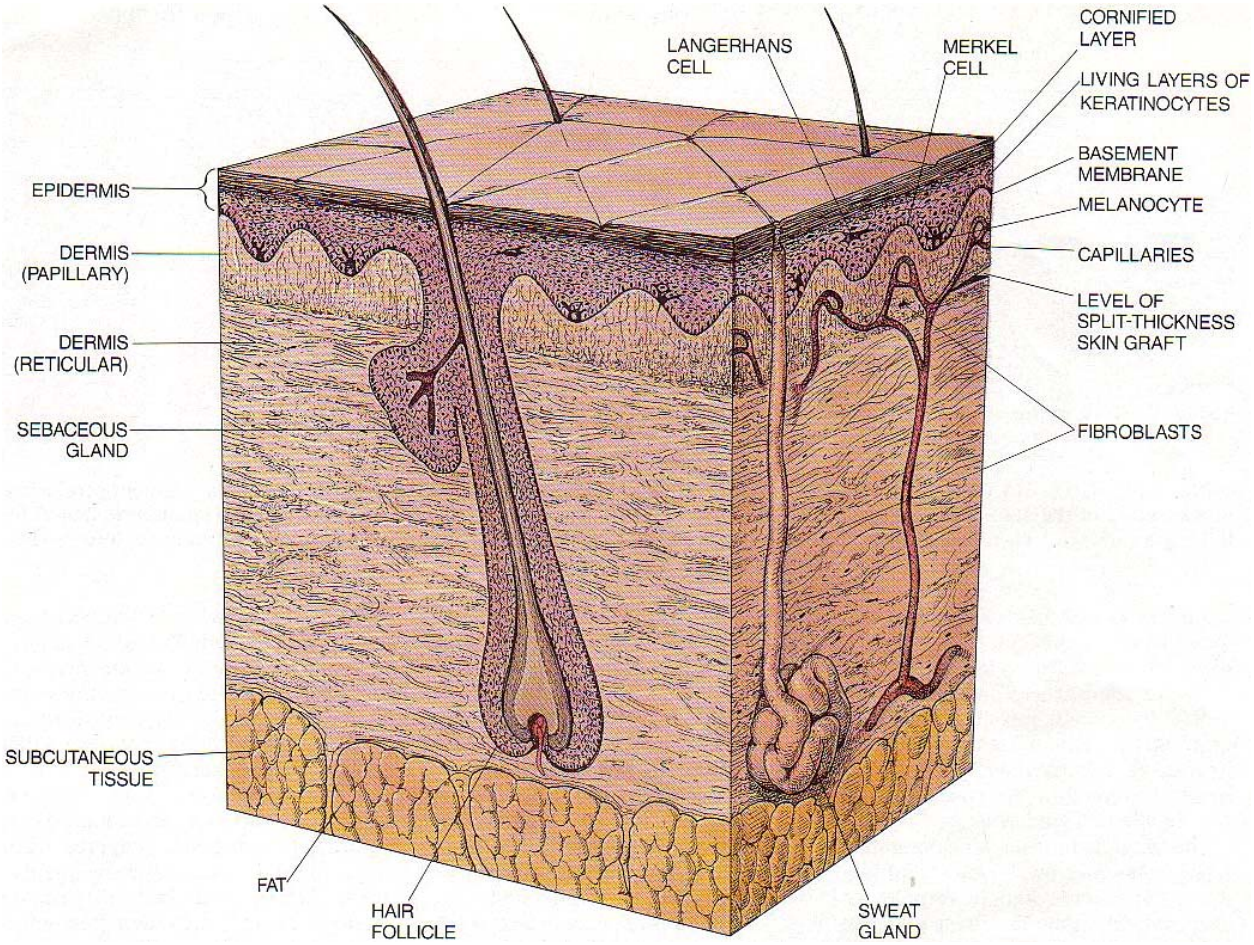


Figure 10.27 Skin includes the epidermis and dermis. Dead keratinocytes, or corneocytes, for the outer part of the epidermis, and living keratinocytes form the inner part. The underlying dermis is composed of fibroblasts and their products, which are organized differently in the papillary and reticular layers (Green, 1991).

pheniramine with undecylenic acid to form a fatty acid salt. The percutaneous absorption of the salt was also reduced. But the absorption of the salt could be enhanced by dissolving in a nonpolar, nonvolatile solvent such as isopropyl oleate (Berner & Kydonieus, 1996).

3. Technical Problems

Problems may arise during the development of transdermal delivery systems. Uniformity of laminated components may vary from batch-to-batch, and the patch components may be migrated or lost throughout the system during storage. In certain cases, a drug contained in polymers may be crystallized in a metastable state to result in polymorphism, which may cause the change in drug release profiles.

C. Criteria of Drug Selection for Transdermal Delivery

1. Potency

First and foremost, the therapeutic agent must be potent. Given that the size of the patch cannot (for practical, economic and cosmetic reasons) exceed, say, 50 cm^2, and given that the barrier function of the skin is the best that the human body possesses, it is not within the capability of existing technology to deliver more than 50 mg of drug per day. The therapeutic agent must be effective when delivered slowly over a relatively long time period.

2. Clinical Need

To be truly useful and to represent a real therapeutic advance, transdermal delivery must confer a real benefit over existing treatment(s). Hence, if the drug has a narrow therapeutic window, is subject to extensive first-pass metabolism when given orally, must be taken several times per day, and causes unpleasant side-effects owing to its short half-life, which leads to highly fluctuating plasma levels, then transdermal delivery has much to offer.

3. Physicochemical Properties

a. Molecular weight and size: Delivery of drugs with molecular weight larger than 500 is not practical. When we compare nitroglycerin and insulin, we can easily see that nitroglycerin will be absorbed through the skin easily while insulin will not.
b. Water solubility: The water solubility of a drug is related to the skin permeability. Hydrophobic drugs are absorbed through the skin much more easily than hydrophilic drugs. For example, steroids will be absorbed better than aspirin. The drugs with octanol–water partition coefficients between 10 and 1000 are likely to have decent passive skin permeabilities.

4. Nonirritant to Skin

Obviously, any transdermal dosage form must be nonirritating to be safe and effective.

5. No Interaction with Patch Component

It is noted that just because a drug satisfies the above criteria does not necessarily make it a good transdermal candidate. If a drug is presently administered orally as a once-a-day tablet with good bioavailability and negligible side-effects, then there will be no possible benefit we can get from the development of a transdermal patch.

D. Enhancers and Excipients (Promoting Skin Permeation)

Despite many advantages of transdermal-controlled drug delivery, this route of administration for systemic delivery presents unique challenges. Since the skin is rate controlling for all commercial systems except the alcohol-containing transdermal estradiol and transdermal clonidine systems, both membrane-controlled and monolithic systems exhibit zero-order release *in vivo* (Berner & Kydonieus, 1996). To overcome the poor permeation through the stratum corneum, permeation (or penetrating) enhancers (mainly surfactants) are often used. Much effort has been directed towards the search for specific chemicals, or combinations of chemicals, that can act as penetration enhancers. The trend in recent years has been to identify substances that are categorized as "generally regarded as safe" (GRAS), rather than the more difficult path of seeking regulatory approval for a newly synthesized enhancer (*i.e.*, new chemical entity). Examples of surfactants are:

1. Anionic surfactants: sodium lauryl sulfate, sodium oleate
2. Cationic surfactants: dodecylamine, stearylamine, cetyltrimethyl ammonium bromide (CTAB)
3. Nonionic surfactants: linolenyl alcohol, polyoxyethylene sorbital

Remember that penetration enhancers will, by definition, reduce skin barrier function, and as a result they must trigger a response in the skin that is designed to correct the effect. The level of irritation accompanied by use of permeation enhancers reflects the extent of the perturbation. This natural response ultimately determines the feasibility and acceptability of the use of enhancers and can influence significantly the form of transdermal product that is developed. There are currently two testosterone systems on the market: (1) Testoderm® (Alza Inc.: Palo Alto, CA) that is a relatively large patch designed to be worn on the shaved scrotal skin of the patient. The application site is relatively permeable, permitting the necessary dose to be absorbed without use of "aggressive" formulation components; (2) Androderm® (TheraTech Inc.: Salt Lake City, UT) that is designed to be worn on almost any body site (*e.g.*, upper arm, chest, etc.) (see Figure 10.28). It is capable of delivering the target dose through inherently less permeable skin by the incorporation of penetration enhancers in the patch. It follows that development of the latter formulation accepted the higher levels of local inflammation (produced as a result of the absorption of the enhancer) in exchange for a significant (expected) improvement in patient acceptability and compliance.

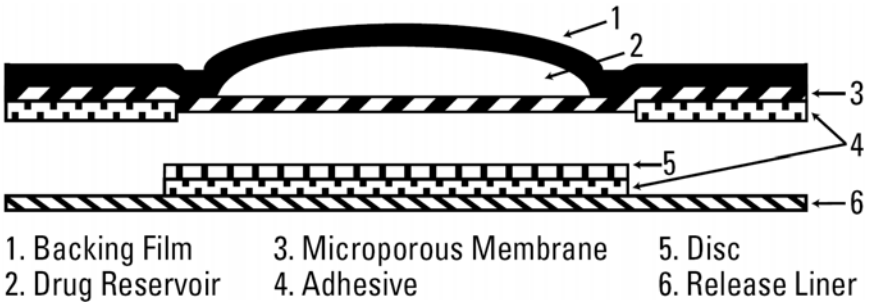


Figure 10.28 Schematic of an Androderm® patch.

Another limitation of the use of chemical enhancers is the lack of control on the permeation of drugs. Typically, between subjects (and even at different sites on the same subject), the variability in permeation can be high; coefficients of variation of ≥ 50% are not uncommon.

E. COMMERCIAL APPLICATIONS

1. Scopolamine Transdermal Patch

Commercial applications of transdermal controlled drug delivery systems started in 1980 with the FDA approval of the first transdermal product, Transderm Scop®. Transderm Scop® delivers scopolamine for prevention of nausea and vomiting associated with motion thickness.

Product Name	Duration	Polymer	Company
Transderm Scop®	2–3 d	EVA copolymer (reservoir device)	Alza/Ciba

2. Nitroglycerin Transdermal Patch

Transderm Nitro was approved by FDA in 1981 for the treatment of angina pectoris.

Product Name	Duration	Polymer	Release Rate	Company
Transderm Nitro®	1 d	Polypropylene (reservoir device)	17.8 μg/cm^2/h	Alza/Ciba
Deponit®	1 d	Lactose (reservoir gradient-matrix system)	13.5 μg/cm^2/h	Schwarz Pharma
Nitro-Dur®	1 d	Cellulose ester (monolithic device)	(17.2 μg/cm^2/h)	Key
Nitrodisk®	1 d	Silicone (monolithic device)	(29.7 μg/cm^2/h)	Searle
Minitran®	1 d	(monolithic device)	0.1–0.6 mg/h ~7 cm^2	3M Ryker

3. Estrogen Transdermal Patches

Decrease in estrogen levels after menopause leads to increased risk of cardiovascular disease and osteoporosis as well as to less severe adverse ef-

fects. The increased risk of heart attack after menopause is due to the decrease in HDL and increase in LDL. The administration of estrogen is known to decrease in cardiovascular disease by 40%. Oral administration of estrogen, however, often results in nausea, vomiting, headache, vaginal bleeding, and breast tenderness. Transdermal delivery of estrogen eliminates most of these undesirable side effects. Furthermore, since the skin does not significantly metabolize estradiol, only 5% of the amount of drug used in oral dosing was required to achieve the same blood plasma levels.

Delivery of estrogen alone, however, is known to increase the risk of breast cancer, uterine cancer, hyperplasia or neoplasia, gallstones, blood clots, and high blood pressure. The study showed that the benefit of estrogen therapy outweighs the risk of estrogen therapy. Thus, estrogen therapy is still recommended.

A product from Eli Lilly & Co. should provide an alternative to many women. Evista® (raloxifene hydrochloride) from Lilly is available for prevention of vertebral fractures in postmenopausal women at increased risk for osteoporosis. Study also showed that co-administration of estrogen with progestin substantially reduces the risk of cancer. Since progestins alone tend to raise LDL and lower HDL cholesterol, combination hormone replacement therapy in postmenopausal women may not have the same favorable lipid effects as estrogen alone. The study showed, however, that postmenopausal women with intact uteri do not need to worry that the progestins will nullify the beneficial effects of estrogen replacement (Grodstein *et al*., 1996). Transdermal patches that simultaneously deliver estrogen (*e.g*., estradiol) and progestin (*e.g*., levonorgestrel) are being developed.

Estraderm®, which delivers estradiol using a reservoir system, was approved in 1986. Estraderm® is used twice a week for the treatment of postmenopausal syndromes and preventing osteoporosis. It was the first product utilizing a skin absorption enhancer. It has a drug reservoir of estradiol and alcohol gelled with hydroxypropylcellulose, an ethylene–vinyl acetate copolymer membrane for zero-order release, and an adhesive formulation of light mineral oil and polyisobutylene.

Progynova® TS is an estradiol transdermal patch manufactured by Schering Corp. Progynova TS® releases approximately 100 μg of 17β-estradiol per day for a week. Progynova TS Forte® releases twice more. The drug reservoir contains estradiol dissolved in alcohol gelled with hydroxypropylcellulose. Estradiol is released from the drug reservoir through the EVA polymer membrane.

Climara®, jointly developed by 3M Pharmaceuticals, Drug Delivery Systems, and Berlex Laboratories, is the first once-a-week patch for treating menopausal symptoms.

Fematrix®, currently marketed in United Kingdoms, Ireland, and South Korea, is a 17-β estradiol patch worn 3–4 d or 7 d as a hormone replacement.

Menorest® is used for the treatment of symptoms associated with menopause. It was developed by Novogyne Pharmaceuticals Inc. and market-

ed by Aventis. The same product is also marketed by Novartis Pharmaceuticals Corp. under the brand name Vivelle®.

CombiPatch® (Novogyne Pharmaceuticals Inc.) was approved for marketing by the FDA. The CombiPatch® is the first hormone replacement therapy in the U.S. to deliver a continuous dose of both estrogen and progestogen transdermally via a single patch.

The CombiPatch® (estradiol/norethindrone acetate) system relieves moderate-to-severe vasomotor symptoms such as hot flashes, night sweats, and vaginal dryness experienced by many postmenopausal women. The new product, developed and manufactured by Novogyne Pharmaceuticals, is marketed by Aventis.

4. Clonidine Transdermal Patch

Catapres TTS® provides continuous systemic delivery of clonidine for seven days at an approximately constant rate for the treatment of hypertension. Clonidine is a potent antihypertensive agent that is delivered orally at 0.1–0.15 mg dose t.i.d. or b.i.d.

Catapres TTS® is a four-layered film 0.2 mm thick, with system area of 3.5, 7.0, or 10.5 cm^2 with the amount of drug released being 0.1, 0.2,

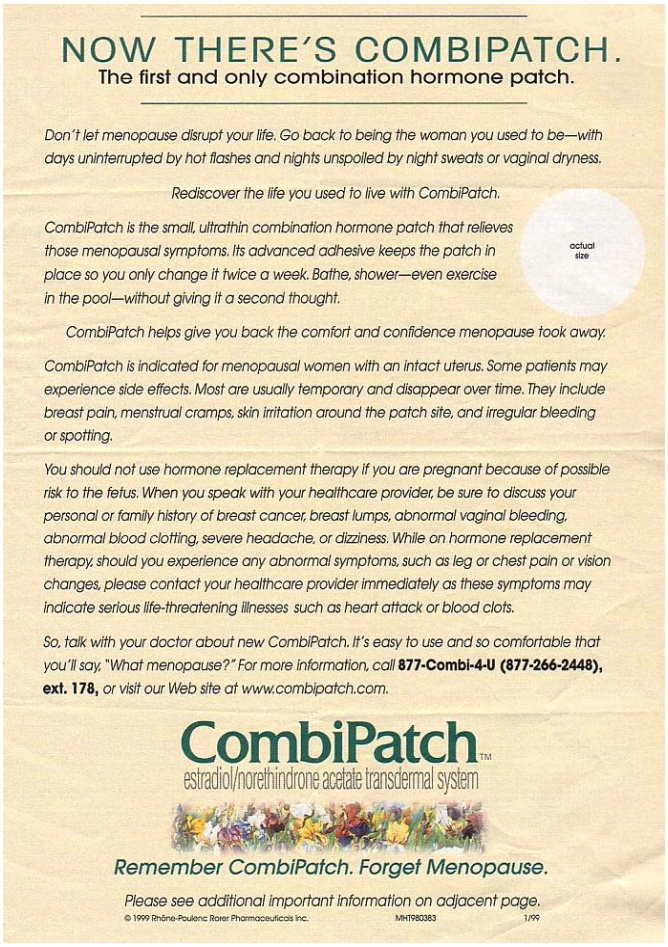


Figure 10.29 Flier (reproduced here at half scale) for Novogyne Pharmaceuticals's CombiPatch®

0.3 mg clonidine per day.

The drug in the reservoir (composed of mineral oil, polyisobutylene, and colloidal silicone dioxide) is released through a microporous polypropylene membrane. Considering the 8–12 hour efficacy obtained by oral administration of tablets, the seven-day efficacy after each transdermal applications remarkably convenient. It also reduces side effects such as reduced drowsiness and dry mouth. Eventually hypertension is controlled with a lower daily dosage of clonidine.

At 24 h after removal of the previous patch and application of a new patch (Catapres TTS®), there is no difference in the mean clonidine concentration owing to an apparent skin depot (Prisant *et al*., 1992).

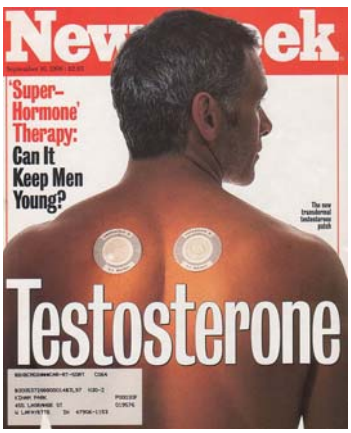
Product Name	Duration	Polymer	Company
Catapres TTS®	7 d	(reservoir device)	Boehringer Ingelheim

5. Fentanyl Transdermal Patch

Duragesic®, also known as fentanyl transdermal therapeutic system, developed by Alza, was approved in 1990 and marketed by Janssen Pharmaceutica in 1991. The patch has a form-fill-and-seal drug reservoir and an ethylene–vinyl acetate membrane for the controlled delivery of the opioid. Fentanyl has a narrow therapeutic index, and the therapeutic level is maintained using a membrane controlled-reservoir system. The reservoir contains the drug in an aqueous ethanolic solution that has the dual purpose of enhancing the permeation of ethanol through skin and reducing the amount of fentanyl by limiting its solubility. This is because fentanyl is an abusable substance. Enhancing permeation by ethanol is necessary since fentanyl has a slow, passive skin transport property. Ethanol, which is used as an absorption enhancer, resides in the drug reservoir. This is to avoid interindividual variation owing to differences in absorption. Thus, the edges of the transdermal patch are sealed.

Duragesic has a activity duration of 72 h and is removed form the skin 24 h after application. The drug remains effective for 72 h since fentanyl has a skin depot effect (Plezia *et al*., 1989). Duragesic® has been approved for use in chronic pain but it has also found to be effective in the treatment of post-operative pain as well. With over 40 million surgical procedures per year, the market for Duragesic® is estimated at $500M.

Product Name	Duration	Polymer	Company
Duragesic®	3 d	(reservoir device)	Jenssen



6. Testosterone Transdermal Patch

Currently there are two commercial products: Testoderm® and Androderm®. Testoderm® (testosterone), which is for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone, was introduced in U.S. by Alza in April 1994. Androderm® is produced by TheraTech in Salt Lake City, Utah.

7. Salicylic Acid Patch

PediaPatch®, Trans-Plantar®, and Trans-Ver-Sal® are over-the-counter dermal patch delivery systems that remove warts. They were developed by Lec-Tech Corp. and marketed by Bradley Pharmaceuticals Inc. The products use patented hydrogel dermal patch technology to provide the controlled-release, site-specific delivery of salicylic acid.

8. Nicotine Transdermal Patch

About 46 million Americans smoke, and eventually, smoking will kill half of them at the rate of over 400,000 a year (Horowitz, 1999). Nicotine stimulates brain cells to release a pleasure-inducing chemical called dopamine. Over 75% of smokers say they want to quit (Horowitz, 1999), and there are novel forms of nicotine replacement (*e.g.*, Nicorette® gum, nicotine-replacement patche, Nicotrol® nasal spray, Nicotrol® Inhaler, under-the-tongue tablet, lollipop, and Zyban®). Zyban®, which is also sold as an anti-depressant called Wellbutrin® SR (*i.e.*, sustained release), lessens the desire to smoke by raising dopamine levels in the brain, just as cigarettes do. With all these aids, however, the one-year quit rate is still less than 20% (Rock, 1999).

The nicotine transdermal patch is a controlled nicotine delivery system in a much more advanced form than cigarette, another nicotine delivery system. When the nicotine transdermal patch was first introduced, it was known as a patch of hope for smokers (at least for a while). The patch delivers a steady fix of nicotine, the addictive part of tobacco, without the 4,000 plus other nasty components that make up tar. The long-term studies are lacking, but the initial data suggest that the patches can double the success rate for quitter in the short run when coupled with behavioral therapy. The nicotine patches may cause skin irritation and sleep disturbances ranging from insomnia to nightmares. Nicotine patch is a prescription drug. Patients must go to the doctor's office and pay for permission to attempt to quit smoking with nicotine patches. To smoke, you don't need any permission; but to quit, you need permission. This does not appear to make sense. One possible explanation is that there is a possibility that nicotine patch may provide a relatively benign way to stay hooked on nicotine and thus result in wide-scale patch abuse. It costs about $100 a month to stay on nicotine patch.

The Nicoderm® patch (Marion Merrell Dow) was the first nicotine patch approved by FDA in 1991. It uses polyethylene-based membrane to deliver 7, 14, or 21 mg/d. It is designed to be applied for 10 wk. The initial ad campaign created a huge demand by the public and it soon outstripped the supply by Marion Merrell Dow. Thus, rival companies could enter the market very easily.

NicoDerm CQ® has been approved as an OTC stop smoking aid. NicoDerm CQ® is the first OTC nicotine patch to be available in all prescription strengths: 21 mg, 14 mg, and 7 mg/d. NicoDerm CQ® provides a step down program that allows smokers to gradually reduce their nicotine intake, rather than stop abruptly. Most smokers should start with Step 1 (21 mg) for six weeks; step down to Step 2 (14 mg) for two weeks; and then

use Step 3 (7 mg) for two weeks. Those who smoke ten or fewer cigarettes a day should start with the Step 2 (14 mg) dose for six weeks and then step down to the Step 3 (7 mg) dose for two weeks. NicoDerm CQ® is the only patch that can be worn for either 16 or 24 h. Smokers who crave cigarettes when they wake up can wear the patch for 24 h.

The efficacy and side effects of nicotine transdermal patches in smoking cessation therapy are shown below.

	Patch	Placebo
End-of-treatment smoking cessation rate	18-77%	1/2 of patch
6-month abstinence rate	22-42%	5-28%
1-year quit rate	20-25%	12%

Product Name	Reservoir	Polymer	Release Rate	Company
Nicoderm® matrix	EVA copolymer (reservoir device)	Polyethylene Merrell Dow	40 μg/cm^2/h	Alza/Marion
Habitrol®	Methacrylic acid copolymer solution in gauze	(monolithic device)	29 μg/cm^2/h	Lohmann Ciba-Geigy
Pro-Step®	Hydrogel	(monolithic device)	130 μg/cm^2/h	American Cyanamid (Elan-Lederle)
Nicotrol®				Parke-Davis (Cygnus-McNeil)

Nicoderm®, Habitrol®, and Pro-Step® deliver nicotine for 24 h. Nicotrol® is designed to deliver for 16 h.

The data show that nicotine patches appear to reduce some, but not all, nicotine withdrawal symptoms. The proper adjuvant smoking cessation counseling is crucial in determining successful long-term outcome with the nicotine patch. It appears that 6–8 wk of patch therapy is an adequate duration for most patients, but more research on optimal duration, dosage, and individualization of patch therapy is needed.

One of the possible reasons that the nicotine patches may not be that effective may be the controlled nicotine release property of the patches. The average cigarette contains 8–9 mg of nicotine and delivers about 1 mg of nicotine systemically to the smoker. Thus, the total amount of nicotine a smoker would get from one pack a day is 20 mg. But real smokers would consume more than one pack a day. The amount of nicotine delivered by cigarette smoking can be much higher depending on the technique of smokers. Because nicotine gum or nicotine patch do not achieve the same peak levels seen with cigarettes, they do not produce the same magnitude of subjective effects as nicotine. In addition, nicotine transdermal patches delivering 20 mg or less of nicotine may result in underdosing of nicotine compared to smoking cigarettes. The transdermal patch methods, however, suppress the symptoms of nicotine withdrawal.

a. Cancer related deaths in the U.S.

The danger of smoking is shown by the extraordinarily high rate of deaths from lung cancer. For males, lung cancer is responsible for 100,000 deaths each year in the U.S. alone. This number is an order of magnitude

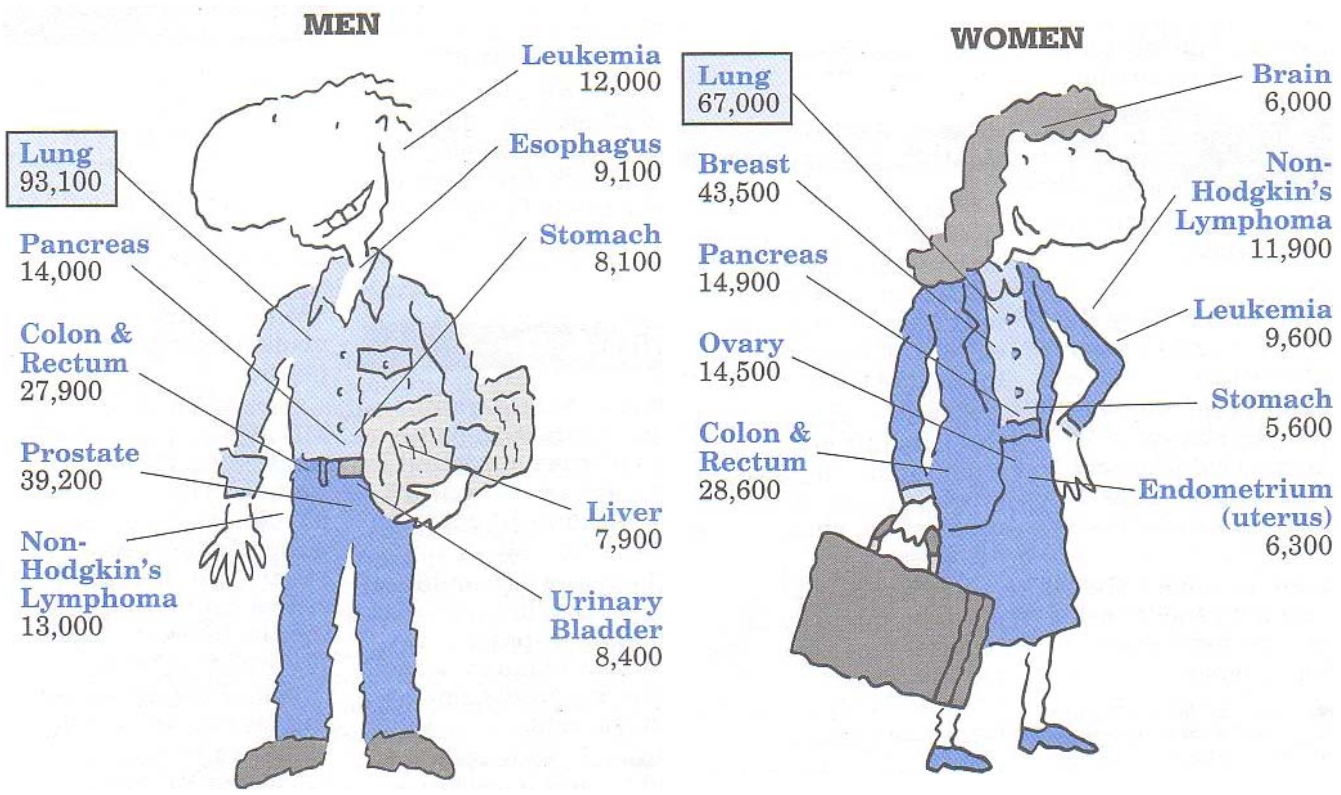


Figure 10.30 American Cancer Society's 1998 estimates of U.S. cancer deaths. Total deaths: 232700 (men), 207900 (women)—difference: 24800 (difference by lung cancer: 26100).

greater than other cancer-related death. In females, breast cancer-related death is higher than other causes, but still lower than the death caused by lung cancer.

b. Information obtained from brochures of nicotine patches

The volume of distribution (V_d) following IV administration of nicotine is approximately 120 L. The major eliminating organ is the liver, and the plasma clearance (PC) is 1.2 L/min. The elimination rate constant, k_{el}, is equal to the plasma clearance rate divided by V_d (*i.e.*, PC/V_d). There is no significant skin metabolism of nicotine, and the plasma nicotine concentrations are proportional to dose for the three dosages of Habitrol® systems. Nicotine kinetics are similar for all sites of application on the back, abdomen, or side.

i. Habitrol®

The following figure shows the plasma nicotine concentrations for two consecutive applications of Habitrol 21 mg/day system. Nicotine concentrations increase to a peak between 6 and 12 hours and then decrease gradually. The pharmacokinetic model which best fits the plasma nicotine concentrations from Habitrol systems is an open two-compartment disposition model with a skin depot through which nicotine enters the central circulation compartment. The nicotine from the drug matrix is released

slowly from the system. Therefore, the decline of plasma nicotine concentrations during the last 12 hours is determined primarily by release of nicotine from the system through the skin.

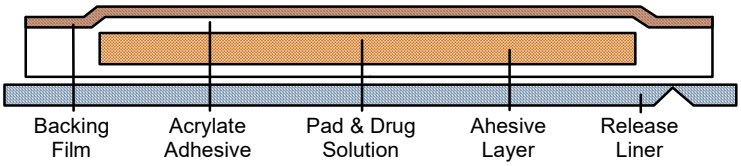


Figure 10.31 Habitrol® systems are round, flat, 0.6-mm thick multi-layer units.

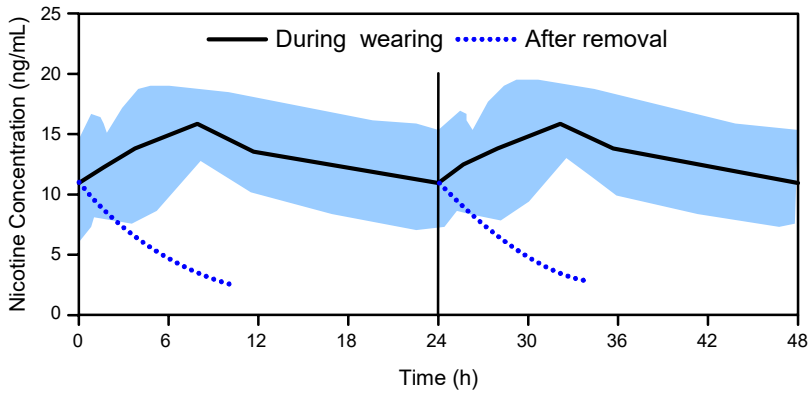


Figure 10.32 Habitrol® steady-state plasma nicotine concentrations for two consecutive 21-mg/d applications (mean ± 2 SD).

ii. Nicoderm®

Figure 10.33 shows a schematic of a Nicoderm® patch. Figure 10.34 shows the plasma nicotine concentrations for two consecutive applications of the Nicoderm® 21 mg/d system. Nicotine concentrations rise rapidly, plateau within 2–4 h, and then slowly decline until the system is removed, after which they decline even more rapidly. The pharmacokinetic model that best fits the plasma nicotine concentrations from the Nicoderm® systems is an open two-compartment disposition model with a skin depot through which nicotine enters the central circulation compartment.

The nicotine from the reservoir is released slowly through the membrane with a release rate constant approximately 20 times smaller than the skin absorption rate constant, as demonstrated *in vitro* in cadaver skin flux studies and verified by pharmacokinetic trials. Therefore, the slow decline

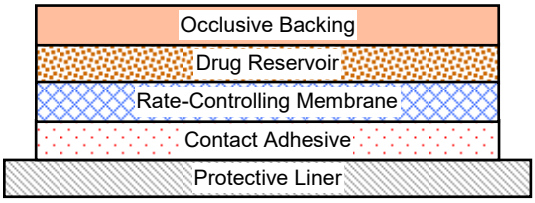


Figure 10.33 Schematic of a Nicoderm ® system (not to scale).

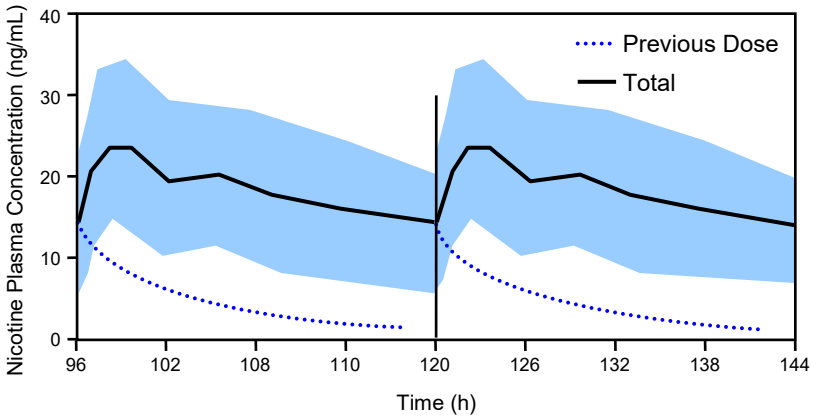


Figure 10.34 Nicoderm® steady-state plasma nicotine concentrations for two consecutive 21-mg/d applications (mean ± 2 SD).

of plasma nicotine concentrations during 4–24 h is determined primarily by release of nicotine from the system. The release from the Nicoderm® to the skin is 20 times slower than the absorption through the skin. The absorption rate of nicotine from the skin depot to blood is slower than the elimination rate.

QUESTIONS RELATED TO NICODERM

(a) What may be the reason to cause the initial rapid rise in plasma nicotine concentrations?
(b) What is the reason for the slow decline of plasma nicotine concentrations during 4 to 24 hours?
(c) The release from the Nicoderm to the skin is 20 times slower than the absorption through the skin. What does this mean?

iii. **ProStep®**

Figure 10.35 show a schematic of the ProStep® system. Figure 10.36 shows the plasma nicotine concentrations for two consecutive applications of ProStep® 22 mg/day system. Nicotine concentrations increase to a peak between 4–12 h and then decrease gradually. The pharmacokinetic model that best fits the plasma nicotine concentrations from the ProStep® systems is an open two-compartment disposition model with a skin depot through which nicotine enters the central circulation compartment.

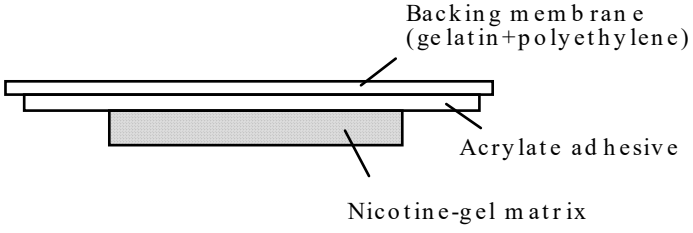


Figure 10.35 Schematic of a ProStep® system (not to scale).

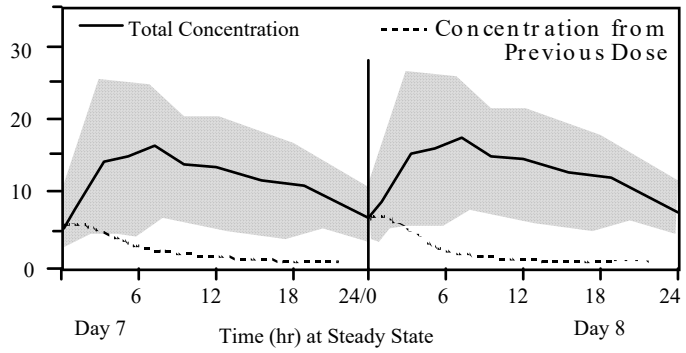


Figure 10.36 ProStep® steady-state plasma nicotine concentrations for two consecutive 22-mg/d applications (mean ± 2 SD)

QUESTIONS RELATED TO ALL THREE PATCHES

(a) Which patch delivers nicotine best? (*i.e.*, largest amount delivered and maintain the highest nicotine concentration in plasma)?
(b) Why does Nicoderm® shows a higher nicotine concentration when the same amount of nicotine (21 mg/day) is delivered?
(c) Which patch delivers nicotine at zero-order?
(d) All of them show the peak and gradual decrease. What is the reason?
(e) If a patch is applied for the first time, which patch is likely to provide a constant nicotine concentration in plasma?

9. Buspirone Transdermal Patches

Once-a-day transdermal patch delivering buspirone (BuSpar™, Bristol-Myers Squibb) was developed by Sano Corp. It may provide a safe and effective treatment alternative for children with attention deficit hyperactivity disorder (ADHD). The eight-week, open-label study showed that 70–80% of patients treated were rated by parents and teachers as "much improved or very much improved." The main advantage of the transdermal patch is that it is applied only once each morning, unlike oral medications that must be taken repeatedly. Furthermore, orally administered drug is metabolized in the liver so that active drug components may be released erratically, creating fluctuations which increase the risk of inconsistent control of symptoms. In addition, side effects of oral drug are associated with the peak drug concentration in blood that may be higher than their therapeutic level. The maintenance of the stable therapeutic levels by transdermal delivery can reduce a lot of adverse effects, and this may be the reason for the tolerability of the transdermal buspirone patches.

F. Physical, Biochemical, and Mechanical Approaches of Enhancing Transdermal Drug Delivery

1. Iontophoresis

Iontophoresis is a process that facilitates the transport of ionic species by the application of a physiologically acceptable electric current (< 1 mA/cm^2). There is good evidence now that manipulation of the current profile can be used to vary the kinetics and extent of drug absorption. Iontophoretic permeation is thought to occur through rare negatively charged pores of 20–25 Å radius (Dinh, Luo, & Berner, 1993). The existence of such pores increases the possibility of peptide delivery (Berner & Kydonieus, 1996). The "downside" is that iontophoresis is not necessarily very efficient; that is, of the total charge introduced, only a fraction is translated into drug delivery, the major part being carried by other ions in the circuit (particularly by small highly mobile species, such as Na^+ and Cl^-, moving out of the body). Therefore, there is an important question of the cost of iontophoresis, in addition to other concerns (for example) of drug stability in an iontophoretic patch, of the extent of skin metabolism and (as for chemical enhancers) of local irritation. Again, one is not going to deliver hundreds of milligrams a day by this route! Indeed, from the iontophoretic data in the literature, it would appear that insulin is too great a challenge. Iontocaine®, the first drug-device combination (Iomed, Inc.: Salt Lake City, UT) was just recently approved.

Drug absorption by iontophoresis may occur by two different ways: ionization and electrolysis; and electro-osmosis (Costello & Jeske, 1995). For the ionization and electrolysis method, drug chosen to be delivered should be ionized. When an electrode contains a solution of ions of the same polarity, they are repelled from the electrode into the body. Anions are repelled from the cathode (negative electrode) and cations from anode (positive electrode). Since ions of the opposite polarity are not transferred into the body, it is important to choose the drugs that have the same polarity as the electrode. During iontophoresis, ions and other substances traverse the skin via passage of water through the skin under the influence of direct current. The water carries with it other dissolved substances. The skin is negatively charged at a physiological pH (it is neutral at pH 3–4), and thus, it enhances migration of cations at the anode. Since water is dragged through the skin during this enhanced migration, any substances dissolved in the water can be carried with the water (Holmes & Ivey, 1997). IontoDex™ is an iontophoretic drug system administration for acute local inflammation (Iomed, Inc.).

2. Electroporation

Electroporation is a drug delivery using transient high-voltage electrical pulses. The transmembrane voltage applied is approximately 1 V for electric field pulses typically of 10 μs to 100 ms duration. In this situation, permeability and electrical conductance of lipid bilayers in either living cells or metabolically-inactive systems (*e.g.*, liposomes) are known to rapidly increase by many orders of magnitude. The membrane changes can

be reversible or irreversible, depending mainly on pulse magnitude and duration. The degree of enhancement achieved *in vitro* is related to the applied voltage, and the number and duration of the pulses. Since it is potentially possible to deliver large peptides, oligonucleotides, and other drugs through the stratum corneum in clinically-relevant amount, this approach may be used for routine delivery of large molecules (*e.g.*, insulin). Very little *in vivo* work, however, has been reported and there is almost no information on the skin toxicity associated with the approach.

3. Sonophoresis

Ultrasound causes mechanical perturbation in an absorbing medium, and mechanical energy associated with the sound field is continuously converted into heat. The thermal change is thought to enhance phonophoretic drug delivery. Through the early 1990s there had been numerous studies that showed that high frequency ultrasound (2–10 MHz at ~1 W/cm^2) could produce modest enhancement of simple molecules. It was then demonstrated that low-frequency ultrasound (~100 KHz) at lower power levels could be used to deliver insulin across rabbit skin *in vivo*, resulting in plasma hormone levels that rose significantly during the application period and a concomitant lowering of blood glucose. A parallel reduction of blood sugar has been confirmed in diabetic rats (using an even lower frequency). There was a dose-response both with respect to time of ultrasound application and to the power used. *In vitro* results also indicated significantly enhanced US-mediated delivery of interferon-γ and erythropoietin (with molecular weights, respectively, of ~17 kDa and ~48 kDa). Despite the excitement that these findings have provoked, it is important to maintain an appropriate perspective until several basic questions are answered with respect to scale-up into man, mechanism of action, "toxicity" in the broadest sense, and economic and technological feasibility (*i.e.*, availability of economical ultrasound transducers).

4. Exothermic Heat-Enhanced Transdermal Transport

Wax: The drug is contained in a suppository base composed of cacao butter, isocacao butter, or triglyceride of a vegetable, saturated, fatty acid that has 12–18 carbon atoms as a base and a permeation enhancer. The base softened at body temperature and release more drugs.

Laser energy-enhanced transdermal transport: Repeated exposure to an excimer laser will increase the permeation rate of skin by more than 100-fold and is almost as effective as tape stripping. An excimer laser produces very brief pulses of intense 193 nm UV radiation from an argon–flurine gas mixture.

Moxibustion: A little pile of dead leaves, ginger, garlic, and similar materials on one's skin is ignited. When the moxa is burnt, these ingredients become vapor in the human body or blood and effectively act on cells. This is one of the methods used in the so-called "alternative medicine."

The alternative medicine collectively indicate the use of acupuncture, herbs, meditation, pray, and energy healing. The control of the body by the mind has been one of the central themes in Oriental medicine. Recent-

ly, there have been so many patients who have benefited from the alternative medicine, that alternative medicine is not so alternative anymore. Acupuncture has been accepted and endorsed by National Institute of Health as an alternative and complementary treatment for a miscellaneous host of ailments.

Figure 10.37 Examples of alternative medicine approaches appearing in the media.

5. Skin Stripping

If the stratum corneum is removed, the relatively large size molecules, such as insulin, can be absorbed through the skin. Again, the issue is not whether insulin can be delivered or not. The issue is whether the delivery is highly reproducible or not so that the patient can rely on transdermal delivery of insulin instead of injection.

6. Reverse Iontophoresis

Reverse iontophoresis is iontophoresis used not for drug delivery but instead used for the relatively noninvasive extraction of "information" from the body for the purpose of classical clinical chemistry. Current passage causes ions and other molecules to move in both directions under both electrodes. Thus, with an appropriate level of assay sensitivity, iontophoresis can be used to "sample" an analyte within the body such as glucose.

Although glucose is not charged, iontophoresis can dramatically increase the passage of this polar sugar across the skin by electro-osmosis. At neutral pH, the skin is a negatively charged membrane, perm-selective to cations. On application of an electric field, more charge is carried across the skin by positive ions than by negative ions. In turn, this means that more momentum is transferred to the solvent in the direction of cation movement. This "electro-osmosis" results in the fact that polar, yet uncharged, molecules, such as glucose, (which have very low passive per-

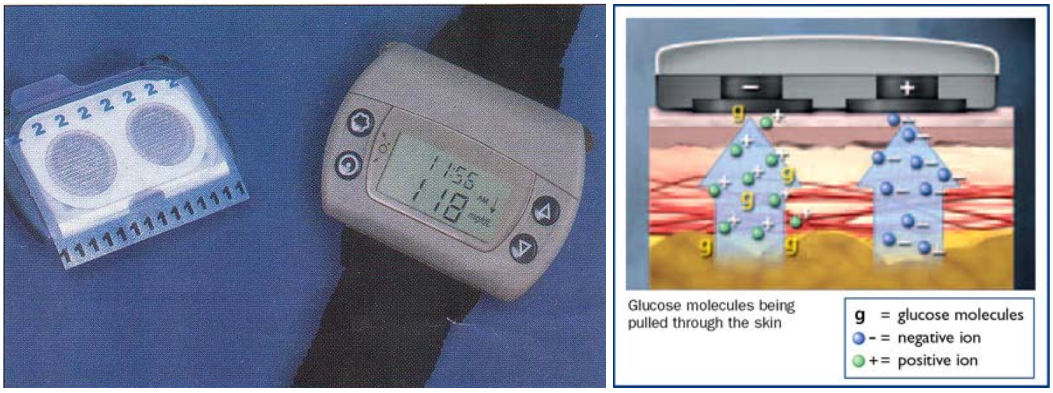


Figure 10.38 The GlucoWatch® Biographer.

meabilities across the skin) can be effectively "carried" across the barrier at significantly elevated rates.

The GlucoWatch® Biographer (Cygnus: Redwood City, CA) provides glucose readings automatically and noninvasive, up to three times an hours. The system consists of two integrated parts: the Biographer and the AutoSensor. The Biographer, worn like a watch, calculates, displays, and stores glucose readings. The AutoSensor is a single-use component that first collects and then converts the glucose into an electric signal. An extremely low electric current is used to pull glucose through the skin. The AutoSensor snaps onto the back of the Biographer and adheres to the skin. It is effective for up to 12 h. The Biographer creates an electronic diary, storing up to 4,000 values that can be reviewed at the touch of a button, helping to detect trends and track patterns in glucose levels. In addition, users can set personal glucose alert levels so that an alarm sounds if readings are too high, or too low, or if readings decline rapidly.

7. Supersonic Powder Injection

Powder injection is a painless, cost effective and easy to use drug delivery technique which can significantly improve the treatment of patients currently injected by needle and syringe. Powder injection functions by accelerating fine particles of powdered drug in a transient supersonic helium jet to provide sufficient momentum that they penetrate dermal or mucosal surfaces resulting in local or systemic drug delivery. A small canister of compressed helium provides the energy source for particle acceleration. Drug is contained in a cassette designed to burst open at a predetermined pressure. A rocket nozzle with a standard convergent-divergent design is used for the acceleration path. An actuation sleeve is used to create sufficient contact with the dermal surface prior to actuation. Upon actuation the helium canister releases compressed gas into an expansion chamber. When sufficient pressure builds, the drug cassettes bursts and the drug particles enter the accelerating gas flow. The velocity of the drug particles is controlled by the design of the nozzle.

This intradermal drug presentation may provide more patient-acceptable delivery of drugs from biotechnology such as proteins and peptides, and also help to realize the potential of gene therapy, for example,

delivery of DNA vaccines to desired skin cell targets. Powder delivery is expected to improve compliance, thus decreasing medical complications and their associated costs. Site-specific administration and the ability to alter pharmacokinetics through powder injection may provide therapeutic advantages for certain drugs.

When testosterone was delivered to rabbits (n = 6) using dermal PowderJect®, the pharmacokinetic profile observed was similar to that of a subcutaneous injection using a needle and syringe. The relative bioavailability observed for powder injection in this example is 55% relative to subcutaneous injection.

8. Microneedles

Micron-sized needles (see Figure 10.39) have been etched into silicon using microfabrication techniques. These microneedle arrays, when inserted into the skin, create conduits for transport across the stratum corneum, the outer layer of skin that forms the primary barrier to transport. Inside the stratum corneum drug molecules can diffuse rapidly through deeper tissue and be taken up by the underlying capillaries for systemic administration. It is to be noted that microneedle arrays can create these transport conduits without causing pain. A similar approach has been used several years ago in Asia where acupuncture is commonly utilized for treatment of various diseases. The study on insulin delivery showed that insulin delivery was increased by orders of magnitude but there were significant inter-individual variations.

9. Macroflux® Transdermal Technology

Macroflux® Transdermal Technology was developed by Alza Corp. for rapid and efficient protein delivery through the skin. Although transdermal drug delivery offers a number of benefits, transport through the skin has many challenges, particularly for proteins and other macromolecules. Macroflux® microarray technology offers a needle-free and controlled transdermal delivery option for rapid and sustained macromolecule delivery. This approach is a variation of the microneedle technology.

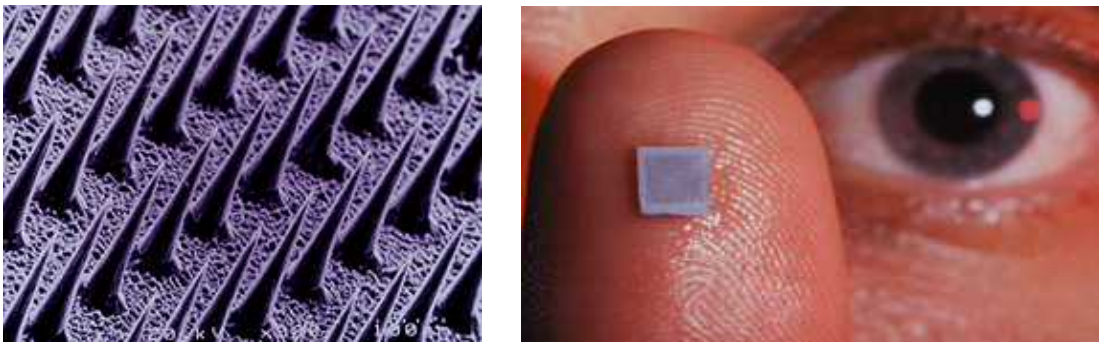


Figure 10.39 A microneedle array (left) designed by scientists at the Georgia Institute of Technology combines the painlessness of a patch with the penetration of needles. One tiny patch (right) contains 400 needles in an array to deliver drugs. The needles poke beneath upper layers of skin, but above nerve endings.

10. Microinfusor systems

a. Infu-Disk™

Infu-Disk™ is a low-cost, continuous flow, noise-free, miniature disposable pump system. The pump delivers fluid at any flow rate between 0.02 and 4.0 mL/h, and the flow rates are factory set. Infu-Disk™ is a totally autonomous delivery system that does not require additional components. The E-Cell™ module (battery) at the heart of Infu-Disk™ pump produces an accurate, continuous flow of oxygen gas, and the pressure within the pump's gas cavity pushes against the diaphragm and expels the delivery fluid.

b. Medipad™

A device has been developed for subcutaneous delivery of drugs in a continuous, intermittent, or pulsatile manner by Elan Pharmaceutical Technologies (Ireland). It is a small, self-adhesive programmable microinfusor drug-delivery system, called Medipad™ (see Figures 10.40–10.42). The delivery device is disc-shaped (5.5-cm in diameter × 1.1-cm thick) and capable of delivering up to 10 mL of drug solution continuously over a 48 h period (Gross & Kelly, 1996; Meehan *et al*., 1996). The drug is delivered to the subcutaneous region through a minute probe, which is hidden from the patient on application of the device. The Medipad™ microinfusor system is divided by a diaphragm into two compartments: the drug reservoir compartment and the compartment containing the electrolytic gas generator with an electronic unit. When the system is activated (by pressing the "START" area), the needle, which is invisible to the user during application, is advanced into the tissue at the proper depth and angle. The volume of drug delivered from the upper compartment is controlled by the amount of gas generated on application of an electrical potential in the bottom compartment.

G. TRANSCUTANEOUS IMMUNIZATION

Most of vaccination is done by injection and, to a lesser extent, by oral administration. Vaccination by transdermal delivery would be another approach which is easier than injection. The skin is designed to protect the body from harmful elements in the environment. Skin is known to be one of the most immunogenic sites that antigens can be delivered to. Transcutaneous immunization requires boosting of immune responses by, for example, using the adjuvant activity of cholera toxin. Alternatively, transdermal patch containing an array of microneedles thinner than a human hair at their base, tapering to microns at their tip, might be used to deliver vaccines below the epidermis. The microneedles are so small that they may not contact pain-inducing nerves.

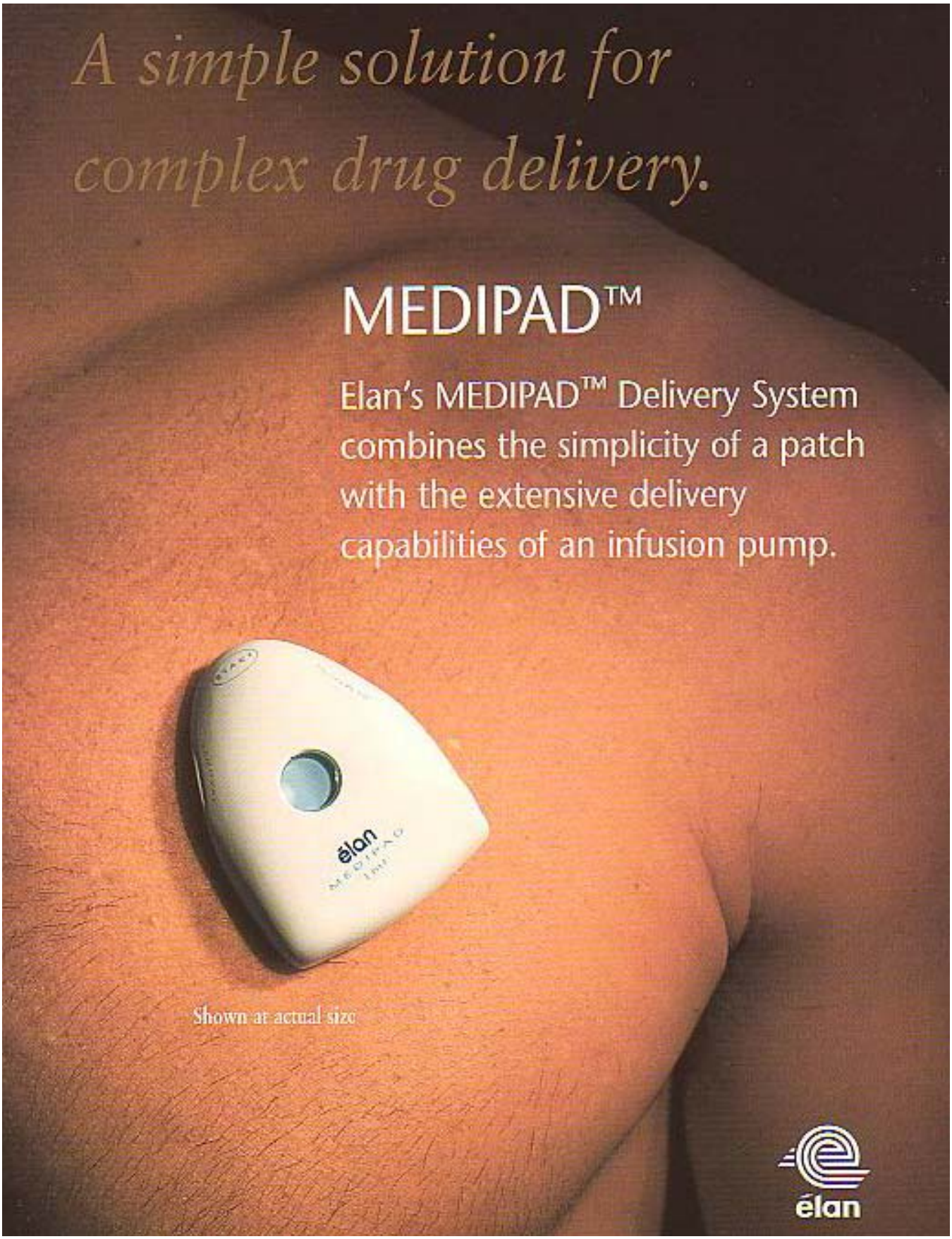
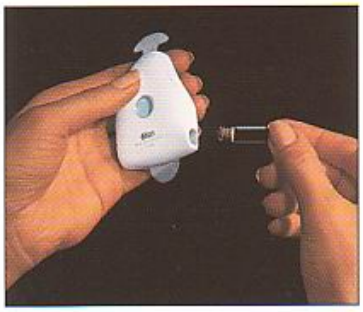


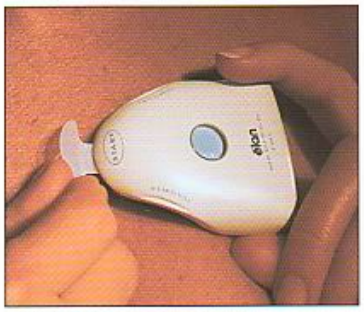
Figure 10.40 Medipad™ (actual size) shown in position and ready to operate.

Four simple steps to use MEDIPAD:



Insert the custom MEDIPAD Drug Cartridge into the system.

Remove the adhesive backing cover.



Apply the MEDIPAD to the application site and remove the safety tab.

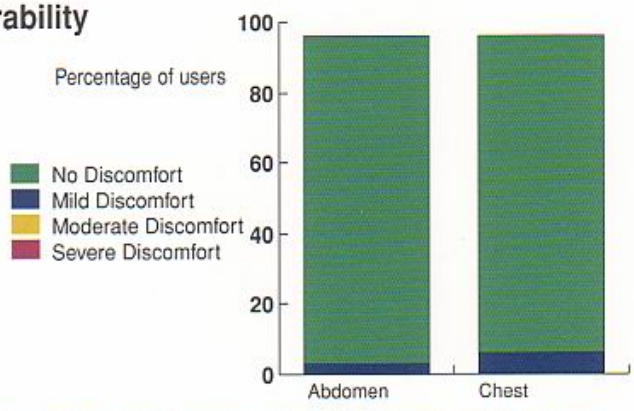
Press "Start" to initiate delivery.

Easy-to-use design facilitates patient acceptance

The MEDIPAD is easy-to-use and requires minimal training. Patients simply push the "Start" button, and the custom programmed system does the rest. Because the system is designed for self-administration by the patient or caregiver in an outpatient or home setting, healthcare costs are minimized. In addition, it is an ideal system for patients on short-term therapy or those with impaired dexterity.

Extensive research has gone into designing a minimally invasive, comfortable needle that provides accurate, consistent delivery. The 3 Position Needle Mechanism ensures proper needle placement. It also minimizes needle phobia since the patient never sees the needle during use. In clinical studies, users consistently rated the MEDIPAD as "very comfortable" and "does not interfere with normal movements."

Tolerability



Users report virtually no discomfort while wearing the MEDIPAD. No users reported moderate or severe discomfort. (Summary of data points over two days of comfort ratings.)

Figure 10.41 Medipad™ instructions.

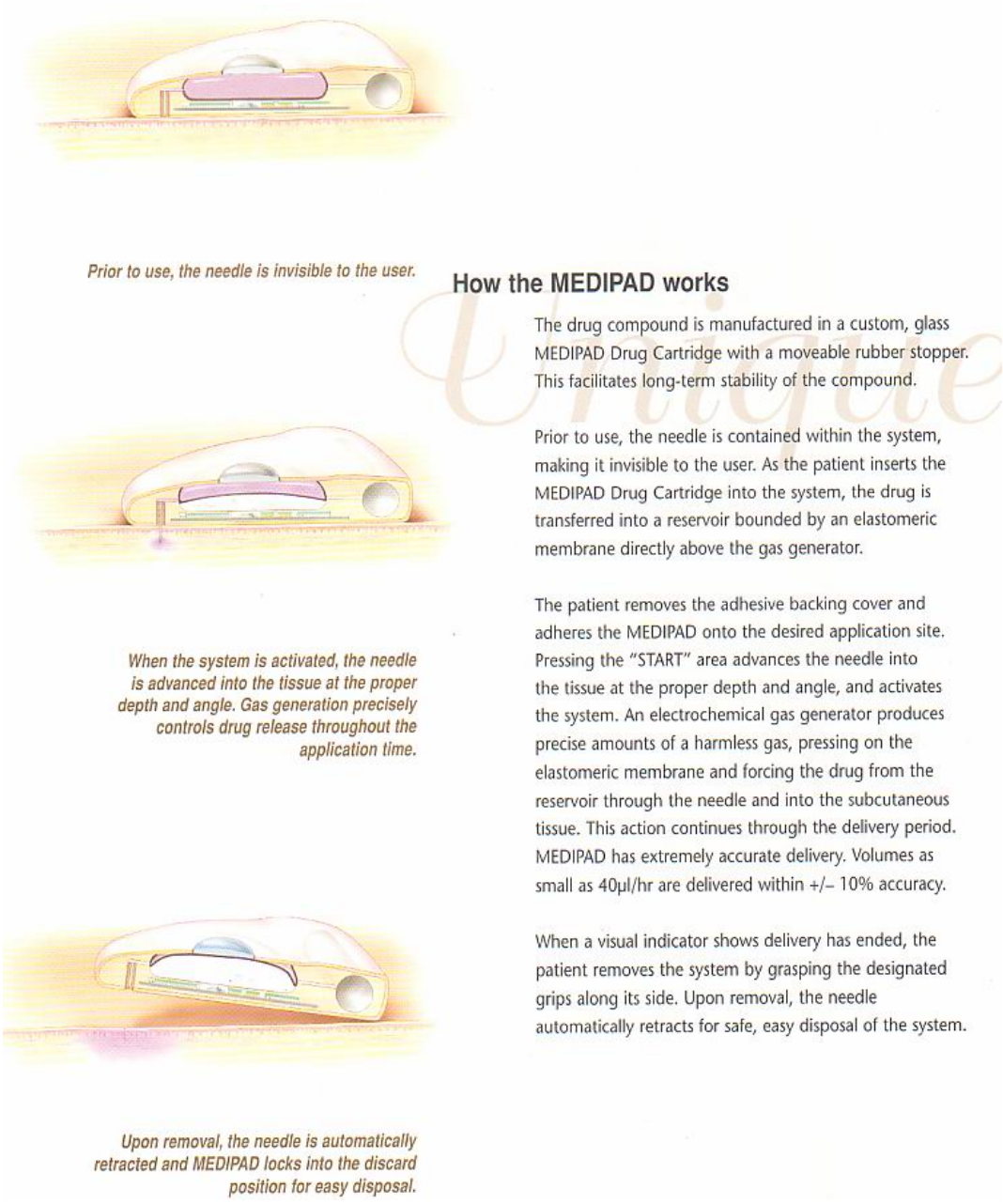


Figure 10.42 Illustration of needle activation of the Medipad™.

H. VETERINARY PRODUCTS

1. Frontline® for Flea and Tick Control

Fipronil is used to protect pets from fleas and ticks. Usually, one application on the skin is enough for controlling fleas and ticks for a month. When a commercial product known as Frontline® is applied to a pet, Fipronil is stored in the natural oils of the pet's skin and coat (see Figures 10.43–10.44), and provides the month-long protection even after a whole lot of baths and shampoos and romping in the rain. Fipronil is then slowly released throughout the pet's body for long-lasting protection.

IV. PARENTERAL CONTROLLED RELEASE DOSAGE FORMS

Drugs which are unstable in the GI tract or too poorly absorbed from the GI tract to provide satisfactory response are good candidates for parenteral administration. The parenteral administration provides rapid absorption of drugs and predictable blood levels. The parenteral route of administration is especially useful in treating patients who are unconscious or unable to accept oral medication. The injectables account for 15% of the dosage forms on the market.

For parenteral administration, the needle has to go through epidermis, dermis, subcutaneous tissue, subcutaneous adipose tissue, and muscle. Thus, parenteral drug delivery can be divided into intradermal (into the skin), subcutaneous (under the skin), intravenous (into a vein), and intramuscular (into a muscle) injections.

The intradermal route is used mainly for the injection of various substances including agents for diagnostic determinations, desensitization, or immunization. Usually only about 0.1 mL may be administered in this manner.

Subcutaneous injections are prepared as aqueous solutions or as suspensions and are administered in relatively small volumes of 2 mL or less. Insulin is an example of a drug administered by the subcutaneous route. Subcutaneous injections are generally given in the forearm, upper arm, thigh, or nates. Newly developed insulin infusion pumps allow patients to achieve and maintain blood glucose at near-normal levels on a constant basis.

Continuous intravenous injection of a drug results in the most effective treatment of a disease by maintaining the constant therapeutic drug concentration as long as necessary. It, however, can be applied only to hospitalized patients or patients with close medical supervision. Advances in infusion technology and computer technology have resulted in devices with extremely sophisticated drug-delivery capabilities, and as a result these cost-efficient devices provide greater accuracy and reliability of drug delivery than the traditional gravity-flow infusion methods.

Aqueous or oleaginous solutions or suspensions may be used intramuscularly. Certain drugs, because of their inherent low solubilities, provide sustained drug action after an intramuscular injection. For instance, one deep intramuscular injection of suspension of penicillin G benzathine results in effective blood levels of the drug for seven to ten days.

All injectable materials must be sterilized. Sterilization means that all living organisms and their spores are completely destroyed and removed from the preparation. Five general methods used for the sterilization of pharmaceutical products are: steam sterilization, dry-heat sterilization, sterilization by filtration, gas sterilization, and sterilization by ionizing radiation.

A. Depot Formulations

A suspension of a drug in a vegetable oil is absorbed much more slowly than an aqueous solution of the same drug. Slow absorption generally results in prolonged drug action. When slow absorption and long-term drug effect is achieved through pharmaceutical means, the resulting preparation is referred to as a depot or repository injection. Depot-type parenteral controlled release formulations are widely used to avoid the potential hazards while duplicating the benefits of continuous intravenous injection, A depot formulation is an aqueous (or oleaginous) suspension or an oleaginous solution that is administered into subcutaneous or muscular tissue. Because of the ability of controlled release of drugs, parenteral depot formulations can maintain relatively constant therapeutic drug level for a long time with reduced frequency of injection. The benefits of the depot formulations over conventional immediate release parenteral dosage forms are reduced drug dose, decreased side effects, enhanced patient compliance, and improved drug utilization. Examples of injectable depot formulations are listed in Table 10.5.

B. Mechanisms of Controlled Drug Release from Depot Formulations

1. Diffusion-Controlled Systems

Solid drugs can be encapsulated within a membrane or dispersed in a matrix which can be made of biodegradable polymers. In general, microparticles are prepared so that they can be injected.

In addition to biodegradable polymers discussed in previous chapters, phospholipids, long-chain fatty acids, and glycerides are also widely used.

The system based on increased viscosity may be assigned to his category, since increased viscosity will retard diffusion of drug molecules and thus can be considered as a diffusion-controlled system. Sucrose acetate isobutyrate (Eastman Chemical Co.) is used to prepare injectable drug delivery systems. Southern BioSystems, Inc. developed a new drug delivery system called SABER (sucrose acetate isobutyrate, extended release) delivery system. The SABER delivery system is a low-viscosity liquid which increases its viscosity rapidly after application (e.g., injection) resulting in high viscosity form. The SABER in high viscosity form is claimed to be adhesive, biocompatible, and biodegradable. The drug release time can be modified from days to weeks.

2. Dissolution-Controlled Systems

The rate of drug release can be controlled by the slow dissolution of drug particles in the formulation or in the tissue fluid surrounding the formulation. The cumulative amount of the released drug, M, under the sink condition is described as

Table 10.5 Partial List of Injectable Depot Formulations

Depot	Brand name	Company

Cyanocobalamin-Zn-tannate suspensions	Depinar®	Armour
Desoxycorticosterone pivalate (Microcrystalline) in oleaginous suspension	Percorten pivalate®	Ciba
Fluphenazine enanthate-in-oil solutions	Prolixin enanthate®	Squibb
Fluphenazine decanoate-in-oil solutions	Prolixin decanoate®	Squibb
Goserelin acetate-releasing biodegradable implant	Zoladex® implant	Zeneca
Insulin-zinc suspensions	Ultralente® Lente®, & Semilente®	Novo
Levonorgestrel-releasing subdermal implant	Norplant®	Wyeth
Leuprolide acetate (Gonadotropin-releasing hormone analog) suspension	Lupron Depot®*	TAP Pharm
Medroxyprogesterone acetate suspensions in PEG 3350	Depo-Provera®	Upjohn
Nandrolone decanoate injection	Deca-Durabolin®	Organon
Growth hormone injectable suspension	Nutropin Depot®	Genentech
Penicillin G-procaine suspensions	Duracillin® Crysticillin® Wycillin®	Lilly Squibb Wyeth
Testosterone cypionate and estradiol cypionate combination in oil	Depo-Testadiol®	Upjohn
Testosterone enanthate	Delatestryl®	Squibb
Testosterone enanthate-estradiol valerate in ethyl oleate BP repository vehicle	Ditate-DS®	Savage
Recombinant human growth hormone	Nutropin Depot®	Genentech + Alkermes

*There have been many complaints on the side effects of Lupron Depot®. The side effects include suicidal depression, body swelling, numbness, joint pain, and memory loss. The exact percentage of women who have side effects is not known yet, but if the complaints keep building up, the safety of the drug needs to be reexamined.

$$M = \frac{S \cdot D \cdot C_s \cdot t}{h}$$

where S is the surface area of drug particles in contact with the medium, D is the diffusion coefficient of drug molecules in the medium, C_s is the saturation solubility of the drug in the medium, and h is the thickness of the hydrodynamic diffusion layer (*i.e.*, boundary layer) surrounding each drug particle. In this approach, the slow dissolution of drug particles is essential. Two approaches are usually used to control the dissolution of drug particles.

a. Biodegradable microspheres

Zoladex® (Table 10.5) is made of biodegradable polymer, poly(lactide-glycolide).

Naloxone delivery system was also developed using a biodegradable polymers. An ideal antagonist for the treatment of narcotic addition and dependence is the one which is free of agonistic (morphine-like) properties and effective for at least 1 wk. Naloxone is known to be a pure narcotic antagonist that does not possess any agonistic properties (*e.g.*, respiratory depression). Naloxone, however, has a very short duration of action owing to the extensive hepatic first-pass metabolism after oral administration. Microspheres of biodegradable polymers, such as poly(lactic acid) or

poly(glycolic acid), containing naloxone and naltrexone were prepared for controlled delivery after injection using a hypodermic needle.

Alkermes, Inc. (Cambridge, MA) has devised two patented injectable sustained-release systems, Prolease® and Medisorb®, to overcome the brief serum half-lives of various biotechnology protein/peptide products. The two systems offer a modulated release of a biologically active agent from biodegradable microparticles. Alkermes has also developed a novel delivery system designed to enable increased drug delivery to the brain by transiently opening the blood-brain barrier. The system, known as the Cereport® system, is claimed to trigger a short relaxation of the tight cellular junctions of the blood-brain barrier when combined with a bradykinin-based peptide.

Alkermes also developed in collaboration with Genentech, Inc., polymeric microsphere-based drug delivery systems to improve patient convenience and compliance, more stable blood levels of drugs and a possible dose reduction. Alkermes has formulated a one-month microsphere system for delivery of human growth hormone (Nutropin®).

b. Formation of salt or complexes with low aqueous solubility.

A water-soluble basic (or acid) drug can be made into a salt with an extremely low aqueous solubility, which provides controlled release properties.

The alkali salt of penicillin G is highly water-soluble. It can be made poorly water-soluble by making penicillin G procaine (C_s = 4 mg/mL) and penicillin G benzathine (C_s = 0.2 mg/mL). Intramuscular administration of penicillin G procaine in a vegetable oil produces a depot effect that sustains the therapeutic blood level of penicillin for 24–48 h. Gelation of this oil suspension with 2% aluminum monostearate further prolongs the therapeutic blood level of penicillin to 96 h.

Regular insulin USP injection usually lasts for 4–8 h, and thus 2–4 injections are required for proper control of diabetes. Insulin activity can be prolonged by complexing insulin with protamine. Protamine is a water-soluble, strongly basic simple protein isolated from the sperm or the mature testes of fish. The protamine–insulin complex is relatively insoluble in tissue fluids at physiological pH, since it has an isoelectric point of pH 7.3. After subcutaneous injection, the protamine–insulin complex slowly releases insulin for up to 24 h. The poor stability of the protamine–insulin complex was improved by forming a protamine–Zn–insulin complex, which provides a prolonged normoglycemic activity more than 36 h. Owing to the low solubility, the protamine–Zn–insulin preparation has a slow onset of action that takes about 6–8 h.

Adrenocorticotropic hormone (ACTH) is a polypeptide hormone that stimulates and regulates the secretion of adrenal steroids, mainly the corticosteroids, from the adrenal cortex. Since ACTH is a polypeptide, it is easily degraded by proteolytic enzymes in the GI tract. It is effective after parenteral administration. The problem is that it is rapidly absorbed from the injection site and has a plasma half-life of only 15 min in human. The effect of ACTH on the adrenals maximamizes when an optimum amount

of the hormone is delivered continuously. The biological activity of ACTH was sustained by formation of ACTH–Zn–tannate complex.

Cycloguanil is the active metabolite of chloroguanide, which has an antimalarial action by inhibiting plasmodial dihydrofolate reductase. It has a short duration of action because of rapid excretion. The palmoate salt of cycloguanil, which has an aqueous solubility of 0.03 mg/mL at pH 7, has the longer duration of antimalarial action.

Naloxone HCl, a water-soluble salt, is effective only for 4 h. On the other hand, the pamoate and tannate salts prolonged the effect to 8 h. The Zn–tannate complex prolonged the antagonistic activity more than 24 h.

c. Suspension of crystals.

In general, a crystal dissolves more slowly as the size becomes larger. This is known as the macrocrystal principle. Crystals, regardless of their sizes, can be used to control the rate of dissolution, and hence the rate of drug release.

Since the dissolution-controlled formulations often result in reduction in the surface area as particles dissolve, the release kinetics is usually not zero-order.

Depo-Provera C-150® (Upjohn) is an injectable long-acting contraceptive formulation made of an aqueous suspension of microcrystalline medroxyprogesterone acetate (150 mg). It is recommended for intramuscular injection deep into the gluteal muscle, one dose every 3 mo.

3. Adsorbent Systems

Peptide and protein drugs tend to adsorb to solid surfaces. The adsorption becomes stronger as the surface becomes more hydrophobic. The adsorbed (bound) drugs and the desorbed (free) drugs are in equilibrium. This means that as the free drugs are removed, the bound drugs are released to keep the equilibrium. This phenomenon can be used to control the drug release using absorbents.

This approach is quite widely used in the preparation of vaccines. Antigens are adsorbed to dispersed aluminum hydroxide gel to prolong the release. ACTH has been also adsorbed onto aluminum phosphate to sustain its biological activity.

4. Prodrug Systems

Drugs can be esterified to form bioconvertible prodrugs that can be formulated in an injectable form. The drug release is controlled by the interfacial partitioning of drug esters to the tissue fluid and the rate of bioconversion of drug esters to regenerate active drug molecules. Examples are listed below. They are all formulated in oleaginous solution.

Testosterone 17β-cypionate	Depo-testosterone cypionate®	Upjohn
Fluphenaine enanthate	Prolixin enanthate®	Squibb
Nandrolone decanoate	Deca-Durabolin®	Orgamn

Testosterone is readily absorbed from the GI tract, but has an extensive hepatic first-pass effect (*i.e.*, it undergoes almost complete degradation in

the liver). Even after parenteral administration in an oleaginous solution, testosterone is quickly metabolized and excreted. The androgenic activity of testosterone was enhanced and prolonged by esterification.

The natural estrogens, such as estradiol, are also subjected to extensive hepatic first-pass metabolism. After parenteral administration estradiol is rapidly absorbed and quickly metabolized, with a plasma half-life of only ~1 h. Estradiol benzoate (Progynon® Benzoate, Schering) is prepared by benzoylation of the 3-hydroxyl group of estradiol. An oil-soluble ester slowly releases the active β-estradiol at the site of intramuscular injection to provide a sustained therapeutic level of estrogen for several days. Although estradiol benzoate has an intrinsic biological activity about half that of natural estradiol, its sustained action makes it more efficacious than estradiol.

In the management of psychotic disorders, patient compliance is most important. For this reason, long-acting injectable antipsychotic preparations have been developed to provide a practical solution to minimize this noncompliance problem Prolongation of the antipsychotic activity of fluphenazine was accomplished by esterification. Examples are fluphenazine enanthate (Prolixin® enanthate, Squibb) and fluphenazine decanoate (Prolixin® decanoate, Squibb).

C. Parenteral Delivery of Peptide and Protein Drugs

Recent advances in recombinant DNA technology and better understanding on the therapeutic roles of specific peptides and proteins have made it possible to develop various peptide-based pharmaceuticals. Table 10.6 lists the representative peptide-based pharmaceuticals and their potential functions as well as biomedical applications.

One of the most widely publicized protein drugs is tissue plasminogen activator (TPA). TPA is a naturally-occurring thrombolytic protein that clears debris from the bloodstream and dissolves blood clots. Genentech produced TPA (Activase™) by recombinant DNA technology for treating patients with heart attacks and strokes.

Many growth factors have been characterized and used for growth stimulation as well as maintaining the viability of a wide range of cell types. Epidermal growth factors are used for the medication of burns and wounds, as well as for cataract surgery and other ophthalmic applications.

Erythropoietin is a circulating glycoprotein type of hormone produced naturally by the kidney and has also been reported to stimulate the production of red blood cells. Epoetin-α, a genetically-engineered form of erythropoietin, was originally approved in 1989 for use in patients with chronic renal failure. It has recently received FDA approval for the treatment of anemia in acquired immunodeficiency syndrome (AIDS) patients on azidothymidine (AZT®) therapy. Two commercial products are Epogen® from Amgen and Procrit® from Ortho.

Table 10.6 Examples of Peptide and Protein Drugs

Peptide and Protein Drugs	Functions and Applications
Cardiovascular-active peptides	
Angiotension II antagonist	Lowers blood pressure

Antriopeptins	Regulate cardiovascular function as well as electrolyte and fluid balance
Bradykinin	Improves peripheral circulation
Calcitonin gene-related factor	Vasodilation
Captopril	Management of heart failure
Tissue plasminogen activator	Dissolution of blood clots
CNS-active peptides	
Cholecystokinin (CCK-8 or CCK-32)	Suppress appetite
β-Endorphin	Relieves pain
Melanocyte inhibiting factor I	Improves mood of depressed patients
Melanocyte stimulating hormone	Improves attention span
Neuropeptide Y	Controls feeding and drinking behavior
Nerve growth factor	Stimulates nerve growth and repair
Gastrointestinal-active peptides	
Gastrin antagonist	Reduces secretion of gastric acid
Neurotension	Inhibits secretion of gastric juice
Somatostatin	Reduces bleeding of gastric ulcers
Immunomodulating peptides	
Bursin	Selective B cell differentiating hormone
Colony stimulating factor	Stimulates granulocyte differentiation
Cyclosporine	Inhibits functions of T lymphocyte
Enkephalins	Stimulate lymphocyte blastogenesis
Interferons	Enhances activity of killer cells
Thymopoietin	Selective T cell differentiating hormone
Tumor necrosis factor	Controls polymorphonuclear functions
Metabolism-modulating peptides	
Human growth hormone	Treats hypopituitary dwarfism
Gonadotropins	Induce ovulation, spennatogenesis, and cryptorchidism
Insulin	Treats diabetes mellitus
Luteinizing hormone-releasing hormone (LHRH)	Induce ovulation in women with hypothalamic amenorrhea
Thyrotropin-releasing hormone	Prolongs infertility and lactation in women who are breast feeding
Vasopressins	Treat diabetes insipidus

(Chien, 1992)

α-Interferon has been used against certain forms of leukemia, Kaposi's sarcoma, and lymphoma (Sales of $600 million in 1997). Interleukin-2, an immunostimulator, has also been used to treat metastatic kidney cancer.

1. Lack of Suitable Delivery Systems for Peptide and Protein Drugs

Laboratory experiments on curing cancer in the mouse model using anti-angiogenic factors, such as angiostatin and endostatin, brought high hope for many patients. Many great expectations resulting from finding new protein drugs, however, are quite often brought down to earth in a short period of time. The public simply pours too much expectation to new findings without realizing that it still takes decade to develop new compounds into clinically useful drugs. One of the difficulties in clinical applications of these new peptide and protein drugs is the lack of suitable delivery systems except for parenteral injection. They are therapeutically effective only by parenteral administration. Parenteral administration of

these drugs could have been highly useful if they have long half-lives. Almost all peptide and protein drugs are extremely short acting, and thus repeated injections are often required to maintain therapeutic efficacy. Some drugs, such as growth hormone, luteinizing hormone-releasing hormone (LHRH), interferons, cyclosporins, and TPA, are therapeutically useful only by following a therapeutic regimen that requires multiple injections daily. This means that therapeutic applications and commercialization of these drugs rely heavily on the successful development of viable delivery systems that can improve their biochemical and biophysical stability and systemic bioavailability. Development of nonparenteral routes of administration, such as oral, nasal, pulmonary, ocular, buccal, vaginal, rectal, and transdermal routes, are highly desirable, but as of now delivery through nonparenteral routes is very difficult, if not impossible. The development of implantable, programmable, and/or self-regulating delivery system is most preferred.

All the difficulties in the delivery of these drugs result from the unique properties of peptides and proteins. The properties that cause difficulties are listed below.

a. Poor tissue permeability

Unlike other smaller molecular weight drugs, peptide and protein drugs are too large to effectively permeate through the cell membranes. The poor tissue permeability is the main problem in the delivery of these drugs via nonparenteral routes.

b. Enzymatic degradation

Peptide and protein drugs are very susceptible to the degradation by enzymes. Thus, in case of nonparenteral administration, they may be degraded even before they are absorbed into the blood stream. Even if they are absorbed, they will undergo fast degradation by enzymes in the blood, and this makes it difficult for them to stay in the blood for long period of time.

c. Poor stability

Peptide and protein drugs have to maintain certain tertiary structures to be effective. The exquisite bioactivity of these drugs result from their ability to bind to receptors, and the ability is lost if the tertiary structures are not maintained.

2. Controlled Delivery Devices for Peptide and Protein Drugs

Controlled delivery of peptide- and protein-based pharmaceuticals for long period of time ranging from months to years requires subcutaneous implantation of the devices.

Polyacrylamide–polyvinylpyrrolidone hydrogels were used to prolong the release of immunoglobulin, luteinizing hormone, bovine serum albumin, insulin, and prostaglandin. Poly(hydroxyethyl methacrylate) (Hydron®) and ethylene–vinyl acetate copolymer were used to deliver macromolecules with molecular weights of up to 2×10^{-6} Da over periods of

longer than 3 mo. However, the reproducibility of release kinetics was poor and was later improved by using a low-temperature solvent casting method. One of the reasons for poor reproducibility is in the drug release mechanism. A large amount of drugs in the powder form has to be incorporated during casting of the polymer matrix to create a series of interconnecting channels of the drugs. Then, water can diffuse into the matrix to dissolve the macromolecular drugs and release them through the channels. This technique also requires the use of organic solvent and is time consuming. These polymeric delivery systems are not degradable.

For implantable devices, biodegradable polymers are very attractive, especially when their degradation products are known to be innocuous or biocompatible. They need not be surgically removed at the end of a treatment. Commonly used bioerodible polymers that have been investigated for the controlled delivery of peptide and protein drugs include copolymers of lactide and glycolide (PLGA), cross-linked serum albumin, and homopolymers of poly(lactic acid) (PLA) or poly(glycolic acid) (PGA). PLGA has been utilized in the development of subdermal implants for the monthly subcutaneous controlled delivery of goserelin (Zoladex® implant, ICI), a potent synthetic analog of LHRH. It has been used clinically to suppress the secretion of luteinizing hormone and of testosterone in patients with prostate carcinoma. One of the problems with use of PLGA and PLA is that they often undergo bulk rather than surface degradation. This makes it difficult to control and predict the delivery rate. For this reason, surface-degrading polymers, such as poly(ortho ester) and polyanhydride, are investigated as alternatives. As we discussed before, the issue of biocompatibility has to be considered for all implantable devices.

3. Overcoming Rapid Clearance from Blood by PEGylation

Many peptide and proteins are susceptible to pre-systemic metabolism and this is not limited to hepatic extraction. Significant intestinal epithelial cell enzymatic activity is the first post-absorptive barrier to achieving therapeutic systemic peptide levels. Unlike many traditional drug candidates, peptides are also highly susceptible to enzymatic degradation in the circulating blood.

One approach used currently for delaying rapid clearance from blood is to graft the peptide and protein drugs with hydrophilic polymer chains such as poly(ethylene glycol) (PEG). PEG grafting is known as PEGylation. The attached PEG molecules inhibit interaction of the modified proteins with other molecules in the blood stream. The PEG modified proteins are disguised from the body's immune system and thus results in substantially increased blood circulation time. The bioactivity of PEGylated proteins is usually decreased by 90%. This decrease in bioactivity can be compensated by substantially enhanced half life. So, overall the PEGylated proteins are equivalently bioactive. Examples of PEGylated protein drugs are listed in Table 10.7, and comparative properties of control and PEGylated interferon are listed in Table 10.8.

One of the limitations of PEGylation is that the modification of proteins with PEG is not easy and purification of the modified proteins is sometimes very difficult. There are always PEG impurities (*i.e.*, difunctional PEG molecules that result in formation of protein aggregates). It was reported that PEG could elicit antibody formation. Antibodies to PEG were raised in rabbits by immunization with monomethoxy polyethylene glycol modified ovalbumin given in Freund's complete adjuvant. In the absence of Freund's complete adjuvant, modified ovalbumin, given s.c., did not elicit any anti-PEG antibody response in rabbits and only a weak response in mice. PEG of 10,000 Da and 100,000 Da given in FCA was found nonimmunogenic in rabbits, and PEG of 5.9×10^{-6} Da, given s.c. to mice, showed no or very poor immunogenic properties. It appears that the antigenic determinant of PEG may be a sequence of 6–7 —CH_2CH_2O— units (Richter & Akerblom, 1983). The possibility that antibodies against PEG forms may prevent continued use of PEGylated proteins.

Table 10.7 Examples of PEGylated Protein Drugs

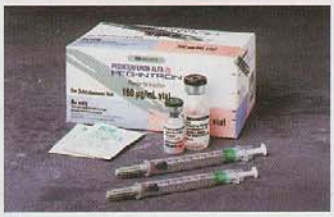
PEG-adenosine deaminase (or 'Pegademase bovine' marketed by Enzon, Inc. as "Adagen") for severe combined immunodeficiency disease (SCID) associated with adenosine deaminase deficiency.
PEG-asparaginase (recombinant asparaginase) (or 'Pegaspargase' developed by Enzon, Inc. as "Oncaspar") for acute leukemias and for lymphomas. Marketed by Rhone-Poulenc Rorer.
PEG- honeybee venom (PEG-HBV) for reperfusion injury associated with organ transplant rejection
PEG-uricase for hyperuricemia assiociated with chemotherapy or gout.
PEG-antigen E for ragweed hay fever
PEG-glucocerebrosidase (Enzon)
PEG-interleukin 2
PEG-interferon (PEGASIS®)

Table 10.8 Pharmacokinetic properties of control and PEGylated interferon.

	Control	Control	PEG 12K	PEGASYS (40K)
V_d	25	30	20	8
Clearance	7700	6000	725	60
Absorption $t_{1/2}$	2.3	2.3	4.6	50
Eliminaton $t_{1/2}$	5.1	8.1	54	65
T_{max} (h)	8–12	8–12	20	80
Dosage Index	Infinite	Infinite	6	1.3

RXPRODUCT NEWS: PIPELINE

A Direct Channel of Information Ali J. Olyaei, PharmD, BCPS



Peginterferon alfa-2b
PEG-INTRON

Introduction

Hepatitis C virus (HCV) is the leading indication worldwide for liver transplantation. In the United States alone, approximately 3.8 million people are infected with this disease, with the most common mode of transmission being percutaneous exposure with contaminated blood product. HIV patients, intravenous drug users, hemophilic patents, and sexually promiscuous patients are at particularly high risk of contracting HCV. In contrast to other forms of viral hepatitis, approximately 85% of patients infected with HCV proceed to a chronic phase.

Serology for HCV (previously known as non-A, non-B) was discovered in the early 1980s. Introduction of interferon-alfa in early 1990 and the approval of ribavirin in the late 1990s were important developments in the hepatology and treatment of HCV. Peginterferon (PEG-INTRON, Schering Corporation, Kenilworth, NJ) is a new formulation of interferon recently approved for the treatment of HCV.[1,2]

Pharmacology

Monomethyl polyethylene glycol (PEG) is a conjugate added to interferon alfa-2b to increase half-life and decrease elimination of interferon. Like other interferons, peginterferon binds to a specific receptor and activates cellular activity of cytotoxic T-lymphocytes and natural killer cells. The pharmacodynamic effect of peginterferon is derived from the interferon alfa-2b moiety, which is obtained from genetically engineered plasmids of *Escherichia coli* bacteria produced from a gene of human leukocytes.[3,4]

Clinical Studies

The safety and efficacy of peginterferon was studied in 1,219 adult patients with chronic hepatitis C infection, including patients with genotype 1 (70%) and patients with a high level of titers (>2 million copies/mL). Patients were randomized to interferon alfa-2b 3 million units three times a week or 0.5, 1, and 1.5 mcg/kg of peginterferon weekly. The patients were treated for 48 weeks and followed for another 24 weeks posttreatment. The primary end point was undetectable HCV RNA and normalization of liver function tests. The overall response rate was similar for the 1- and 1.5-mcg/kg peginterferon groups. However, these groups had significantly better response rates compared with the interferon alfa-2b group. The reported virologic response was 25% for peginterferon 1 mcg/kg, 18% for 0.5 mcg/kg, and 12% for interferon alfa-2b 3 million units. Additionally, 29% of peginterferon patients experienced normalization of liver function tests compared with 18% of the interferon alfa-2b group.

In another study, the safety and efficacy of peginterferon and interferon alfa-2b in combination with ribavirin was studied in adult patients with hepatitis C infection. Fifty-two percent of patients had undetectable HCV RNA after 24 weeks of treatment with peginterferon and ribavirin, compared with 46% in the interferon alfa-2b and ribavirin protocol. In patients with genotype 1, the overall response rate was 41%. In a small pilot study, sustained response was only 65% in patients with HCV and HIV infection receiving peginterferon and ribavirin. After 6 months of therapy, 82% of the patients had normalized liver function tests.[5,6]

Adverse Side Effects

The overall side-effect profile of peginterferon with or without ribavirin is similar to interferon alfa-2b therapy, with the most common adverse reactions including flu-like symptoms, psychiatric disorders, depression, anemia, neutropenia, thrombocytopenia, and thyroid dysfunction. Patients should be counseled very carefully concerning the route of administration and about taking acetaminophen and diphenhydramine 30 minutes before each dose at bedtime.[5,6]

Outlook

Approximately 85% of patients diagnosed with HCV will proceed to a chronic stage and may require treatment. The use of peginterferon in combination with ribavirin will be the standard of practice in chronically infected patients. Without any treatment, most patients will develop end-stage liver disease or die from hepatocellular carcinoma. HCV kills approximately 10,000 patients every year. PT

For a list of references, send a stamped, self-addressed envelope to: References Department, Pharmacy Times, 1065 Old Country Road, Suite 213, Westbury, NY 11590; or send an e-mail request to: References@pharmacytimes.com

Figure 10.44 An article about PEGylated interferon α-2b.

D. PREFILLABLE SYRINGES

Prefilled syringe technology (from Schott) provides convenience, time-savings, greater safety, and reduced waste. Schott Parenta® prefillable syringe offers a packaging system that is appropriate for any product that can be filled into a vial. Meridian Medical Technologies also makes prefillable syringes.

E. NEEDLELESS INJECTABLE SYSTEMS

Recently, needle-free injection systems were developed. The availability of improved technology for self-administration of injectable drugs is expected to improve patience compliance, as well as provide added flexibility in the development of dosage regimes. Needleless injections can achieve greater initial serum concentrations than standard needle inections (see Figure 10.45).

1. PowderJect®

In the PowderJect® Technology (Oxford, UK), fine particles of powdered drug are accelerated to supersonic speed in a transient supersonic helium jet to provide sufficient momentum that they pass through and into the skin for local or systemic effect. A small (5 cm^3) canister of compressed helium provides the energy source for particle acceleration, and a cassette containing drug powders is designed to burst open at a predetermined pressure. A rocket nozzle with a standard convergent-divergent design is used for the acceleration path, and an actuation sleeve is used to create sufficient contact with the dermal surface prior to actuation. It also comes in a mucosal format.

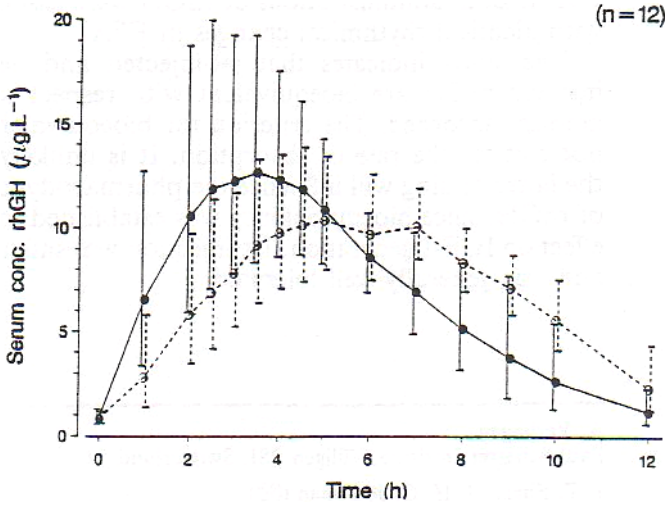


Figure 10.45 Serum concentrations of rhGH (geometric mean with SD) after single-dose subcutaneous administration of 5 IU rhGH by jet injection (—●—) and needle injection (···○···). Levels of rhGH were below the lower limit of quantitation (1.50 $\mu g \cdot L^{-1}$) in all subjects at 16, 20, and 24 h after dosing (Verhagen *et al.*, 1995).

2. Medi-Ject®

Medi-Jector®, a needle-free drug delivery system from Medi-Ject Corp. (Minneapolis, MN), uses an internal spring (which is compressed by turning the end of the device) and compressed carbon dioxide in a cartridge, respectively, as power sources. Medi-Jector Choice® is used for insulin delivery and looks somewhat like a pen. The full drug dose can be seen and the medication vial is attached with an adapter until the device indicates the proper dosage allowing for better dosage accuracy.

3. Biojector®

Bioject Inc.'s (Portland, OR) Biojector® (needle-free injection management system) is a multiple-use needle-free injector powdered by a CO_2 cartridge. Like many needle-free injection systems, it can be administered intramuscularly or subcutaneously. Biojector® 2000 has been used to deliver a number of drugs, such as lidocaine, morphine, heparin, yellow fever vaccine, hepatitis A and B vaccines, and genes.

4. Vitajet®

Vitajet®, another needle-free injection device, was developed to deliver insulin.

5. Bio-Set®

Bio-Set® is a new needleless system for drug reconstitution from Biodome America. Bio-Set® fits standard vial and stopper.

6. Intraject®

The Intraject® needle-free injector is from Meridian Medical Technologies.

V. NASAL CONTROLLED-RELEASE DOSAGE FORMS

Drug delivery through nose may not be unfamiliar to many of us. Many psychotropic drugs and hallucinogens have been delivered through nasal route for centuries. A majority of commercial intranasal products in the past were prepared for decongestion of nasal mucosa. Recently, nasal formulations for other applications have been developed. The nasal mucosa is relatively "leaky" compared to the GI tract, and for this reason the nasal cavity provides an alternative route for the delivery of drugs that show poor absorption following oral administration. Indeed many drugs are shown to have improved bioavailability by nasal delivery than by oral administration.

A. Advantages of Nasal Delivery

Nasal drug delivery offers the several advantages as listed in Table 10.8. For those who have allergies, nasal or sinus conditions, and asthma, drug delivery by nasal route is not only inconvenient but also ineffective.

Table 10.8 Advantages of Nasal Drug Delivery

Both local and systemic effects
High permeability of nasal mucosa compared to the mucosa in the GI tract
Highly vascularised subepithelial layer (faster absorption and onset of action)
Large surface area for absorption
No first pass effect
Pulsatile delivery possible

B. Examples of Nasal Formulations

1. Stadol NS®

Stadol NS® is a nasal spray formulation of analgesic butorphanol tartarate approved in 1992. It was developed by Nastech Pharmaceutical Co. and sold by Bristol-Myers Squibb. The nasal form offers rapid systemic absorption, lower required dosage, and quicker onset of effect.

2. Ener-B®

Ener-B® is a vitamin B_{12} supplement in a nasal gel formulation that was developed by Nastech Pharmaceutical Co., Inc., and is marketed over the counter by Nature's Bounty Inc.

3. Nicotrol NS®

Nicotine nasal spray system (Nicotrol NS® by McNeil) was approved by the FDA in March 1996. One squirt of Nicotrol NS® delivers 0.5–1 mg of nicotine, approximately the same as one Benson & Hedges 100. Since nicotine is rapidly absorbed across the nasal membranes, the nasal spray is thought to provide a kick that is more like smoking. The rapid onset may be effective for reducing craving, but it may have a greater potential for addiction than the slower acting gum and patch (Fiscella & Franks, 1996).

4. Nasal flu spray

The nasal flu spray made of a weakened live flu virus (Aviron Inc.: Mountain View, CA) triggers a strong response in the mucosal linings of the respiratory system, but it also causes a weak blood serum response and a limited cytotoxic T cell response against invaders (Smaglik, 1998). Considering the fact that flu kills 20,000 people a year, the more convenient

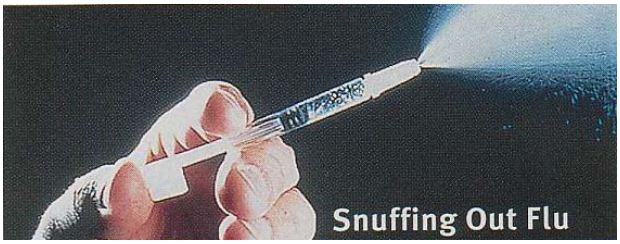


Figure 10.46 The spray vaccine, administered by doctors or nurses, is at least as effective as flu shots. In clinical trails, only 1% of the 1,070 children who received the spray got the flu.

method of flu vaccination than the shot is expected to provide much improved protection and thus save many lives.

5. Nasonex

Nasonex® (mometasone furoate monohydrate) Nasal Spray 50 μg is marketed by Schering-Plough Corp. for treatment of the nasal symptoms of seasonal and perennial allergic rhinitis in children as young as 3 y of age. It is the only nasal inhaled corticosteroid approved in the U.S. for this indication. The usual recommended dose of Nasonex® Nasal Spray for children 3–11 y of age is one spray (50 μg per spray) in each nostril once daily. For adults and children 12 y of age and older, the usual recommended dose is two sprays (50 μg per spray) in each nostril once daily.

The approval for use in growing children is significant, since they have medical considerations quite different from those of a mature adult. Long-term clinical studies were conducted that showed no statistically significant effect on growth velocity in children ages 3–9 y compared to placebo. Nasonex® has a virtually undetectable level of absorption into the bloodstream. The overall incidence of adverse events was comparable to placebo and did not differ significantly based on age or sex. Allergic rhinitis affects more than 6 million children each year and accounts for 2 million missed school days, with indirect costs reaching $4 billion. Day-care centers and schools are environments where exposure to allergens such as dust mites, mold and pet dander carried from home on children's clothing can be particularly high.

C. Nasal Delivery of Peptide and Protein Drugs

For small molecules the above advantages may hold. For large molecules such as peptide and protein drugs, however, nasal delivery may not work. As we discussed before, a major limiting factor in the full exploitation of therapeutically active peptide and protein drugs is the lack of the availability of appropriate delivery systems. Oral administration of protein drugs (*e.g.*, insulin) is difficult owing to enzymatic degradation and poor absorption from the GI tract, and transdermal delivery may not be possible for some of the larger molecules. Thus, efforts have been made to deliver protein drugs through nose.

A nasal insulin delivery technology (known as Nazdel® nasal membrane permeation technology) was developed more than a decade ago. The technology relied on a permeation enhancer, sodium taurodihydrofusidate to deliver insulin. Eli Lilly & Co. licensed the technology only to abandon it several years later.

Many studies have shown that the blood glucose level can be reduced by nasal delivery of insulin in animal experiments. Delivery of insulin and reduction of glucose levels in animal study is not the issue however. The issue is whether the proposed delivery system results in consistent, reproducible clinical effects. Most of the proposed techniques are not reliable. For example, the diabetic patients who got cold may have difficult time to deliver enough insulin through nose.

The use of penetration enhancer for the delivery of insulin may not be a good idea since it has to be used chronically. This means that the mucus membrane will be irritated all the time. Another problem of nasal delivery for systemic effect is that the amount of mucus on a patient's nasal membrane might affect the uptake of drug. Nevertheless, the following drug products have been prepared for the delivery by the nasal route: calcitonin, oxytocin, vasopressin, desmopressin, and LHRH agonists. It should be noted that the bioavailabilities of the above drugs are very low.

D. Physicochemical Properties of Drugs for Nasal Delivery

1. Molecular Size

The nasal absorption is known to fall off sharply when the drug molecular weight is 1,000 Da or greater. By comparison, oral absorption decreases dramatically when the molecular weight is larger than 400 Da.

2. Drug Lipophilicity

It is well known than the drug permeation through the cell membrane is related to the lipophilicity that is measured by the octanol–water system. The higher the lipophilicity, the greater is the permeation. In nasal delivery, however, this does not hold. A series of studies on nasal delivery using barbiturates and progestational steroids indicated that transnasal permeation behavior of drugs may not be predicted by the lipophilicity.

3. Solution pH

For the delivery of insulin, it was noticed that the reduction in plasma glucose levels in dogs depended on the pH of the insulin solution administered intranasally. The maximum effect was observed when the pH was 3.1, while only a slight effect was observed at pH 6.1. Since insulin has an isoelectric point at pH 5.4, the better absorption at pH 3.1 is expected to be due to the enhanced absorption resulting from preferential binding of positively charged insulin to the negatively charged nasal mucus.

E. Approaches for Improved Nasal Delivery

For nasal delivery, the retention of the drug in the nasal cavity is important since premature removal from the nasal cavity would result in no drug absorption at all. For this reason, use of a platform provides advantages. Mucoadhesives, such as poly(acrylic acid), have frequently used to enhance the bioavailability of protein drugs such as insulin. Other polymers, such as methylcellulose and starch, have been used to prolong the nasal residence time of the dosage forms.

VI. OCULAR CONTROLLED RELEASE DOSAGE FORMS

The ocular route is mainly used for topical delivery of drugs to tissues around the ocular cavity. Eye drop solutions are most widely used for ocular drug delivery. The main disadvantage of ocular delivery using eye drops is that more than 95% of the applied drug is lost by drainage. Only

a fraction of the applied drug is absorbed into the aqueous humor. In addition, the second eye drop may wash the first eye drop out of the eye.

To obtain the therapeutically effective drug levels, relatively high concentration of drug solution needs to be instilled frequently to maintain the adequate blood concentration of the drug for long period of time. It is not unusual to see the drug concentration surging to a peak value, which may be higher than the maximum therapeutic level and decline exponentially thereafter.

A. Factors Affecting Intraocular Bioavailability

1. Limited Ability of the Ocular Cavity to Hold Drug Solution

When eye-drop solutions are applied, we tend to apply much more than necessary. A majority of the applied solution is removed immediately from the eye simply by blinking. Only a fraction of the eye-drop solution remains. Patients' error and imprecise measurement result in large fluctuations in dosing.

2. The Presence of Lacrimal Fluid

The drug solution instilled into the precorneal area of the eye can be diluted by lacrimal fluid in the cul-de-sac. The continual inflow and outflow of lacrimal fluid can cause a significant loss of applied drug.

3. Nasolacrimal Drainage

Lacrimal fluid is removed from the eye through the efficient nasolacrimal drainage. An instilled drug solution can be drained away from the precorneal area through this conduit.

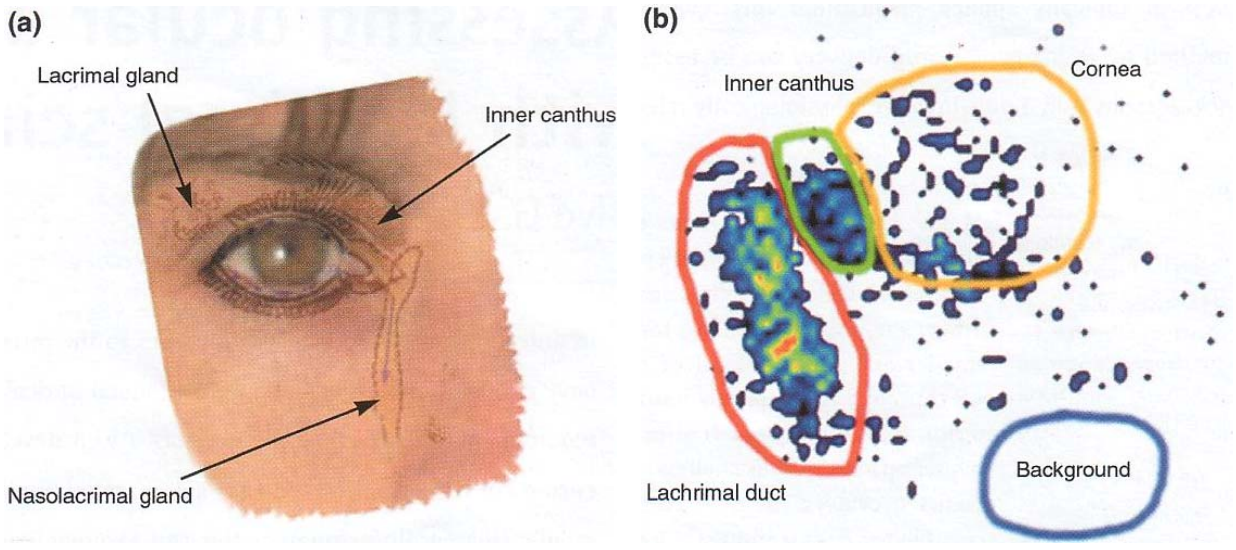


Figure 10.47 (a) The drainage system of the eye. The thin walled duct permits the rapid system adsorption of drug placed in the eye. (b) The generation of four main regions of interest (ROI) in the eye: cornea, inner canthus, lacrimal duct, and background.

4. Protein Binding

Lacrimal fluid normally contains various substances including proteins such as lysozyme and mucin. They can interact and/or degrade the drugs introduced into the ocular cavity.

5. Nonproductive Absorption

The topically applied drugs may be absorbed into various ocular tissues, most notably the cornea and conjunctiva. If conjunctiva is not the target for the drug, then the absorption of the drug will not produce desired pharmacological effect.

B. Approaches for Improved Ocular Drug Delivery

Since the therapeutic efficacy of an ophthalmic drug depends primarily on the exposure time of the drug to the corneal surface, various approaches have been used to increase the contact time.

1. Use of Drug Suspensions

One way to overcome the immediate loss of applied drug is to use drug suspension. Hydrocortisone acetate and prednisolone acetate are marketed as suspension dosage forms. One drawback of the suspension dosage form is that the dissolution of drug particles depends on the quantity of lacrimal fluid. Constant inflow and outflow of lacrimal fluid may not be easy unless one is in a very sad mood.

2. Use of Viscosity-Enhancing Agents

Polymers such as methylcellulose can effectively increase the viscosity of the ophthalmic drop solutions. Drugs can also be incorporated into the water-insoluble ointment formulation. These approaches, however, resulted in only marginal improvement in bioavailability compared to ordinary eye-drop solutions. Increasing viscosity obviously did not increase the contact time with the corneal surface.

3. Ocusert® System

The Ocusert® system (or ocular therapeutic system) is the first ocular delivery systems utilizing the controlled release technology. The Ocusert® system is an oval flexible ocular insert that consists of a core reservoir made from complexation of pilocarpine with alginic acid sandwiched between two sheets of a transparent, lipophilic rate-controlling membrane of ethylene-vinyl acetate copolymer. Figure 10.47 shows a Pilo-20® unit that contains 5 mg of pilocarpine. The Pilo-40® unit measures 5.5 × 13 mm on its axes, 0.5 mm in thickness, and contains 11 mg of pilocarpine.

When an Ocusert® is inserted in the cul-de-sac, the pilocarpine molecules are dissolved in the lacrimal fluid penetrating into the system and released through the EVA copolymer membranes following zero-order kinetics. The release rates can be varied by changing the composition and thickness of EVA copolymer membranes. Pilo-20® and Pilo-40 units are programmed to release pilocarpine at 20 μg/h and 40 μg/h, respectively.

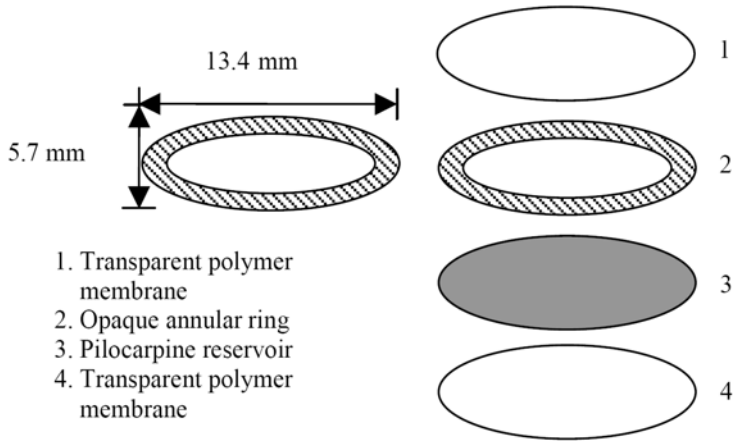


Figure 10.47 Ocusert® ocular insert system for treatment of glaucoma

Figure 10.48 shows the *in-vitro* release of pilocarpine from an Ocusert Pilo-20® system. It shows initial burst release followed by the zero-order release profile as expected from the diffusion-controlled reservoir systems. From the information given in the figure, we can calculate the steady-state release rate from the Ocusert Pilo-20®. Although the Pilo-20® is designed to release pilocarpine at 20 μg/h, the actual steady state release rate is smaller according to the data. (Calculate the steady state release rate: *M* is the cumulative amount of pilocarpine released from the Ocusert Pilo-20® system).

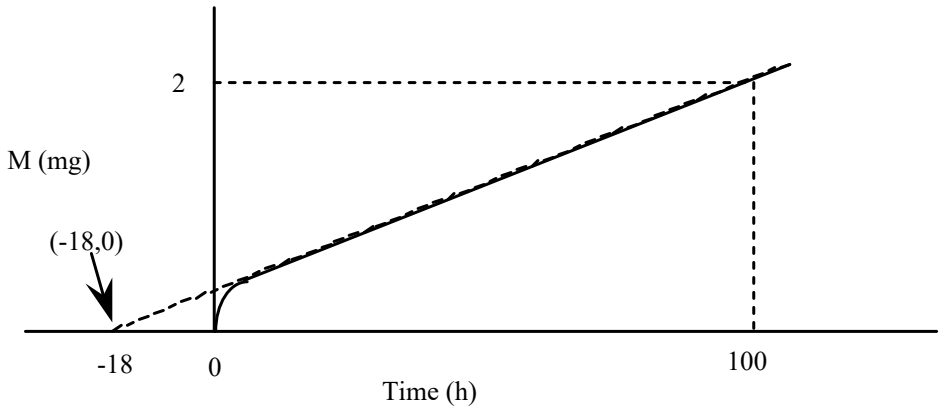


Figure 10.48 *In-vitro* release of pilocarpine from an Ocusert Pilo-20® system.

A typical *in-vivo* release-rate profile of pilocarpine from the Ocusert Pilo-20® system also shows a burst release during the first several hours as shown in Figure 10.49. Initially, the system releases pilocarpine at a rate three times greater than the programmed rate of 20 μg/h. The release rate is maintained within ± 20% of the programmed rate during the remainder of the 7-d treatment period. The system administers a total of less than 70% of the pilocarpine loading dose to the eye at the end of the 7-day medication. The disadvantages of Ocusert are conjunctival irritation, mio-

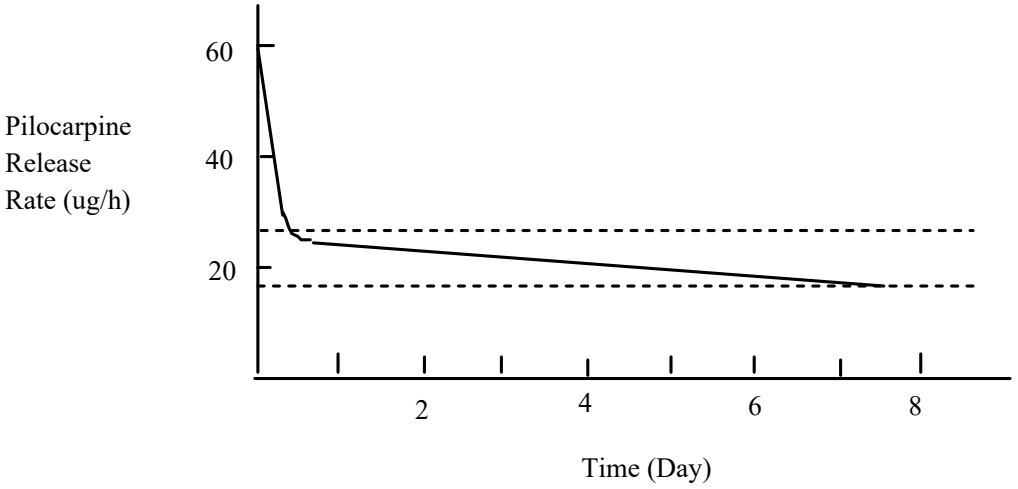


Figure 10.49 *In-vivo* release rate-profile of pilocarpine from an Ocusert Pilo-20®.

sis, and eyelid spasms. Patients with loose eye lids have had difficulty in retaining this device.

4. Ocufit SR® System

The Ocufit SR® technology, developed by the West Company (Lionville, PA), is designed to overcome common problems associated with drug delivery to the eye. Ocufit SR® is a flexible rod-shaped insert, 25 mm in length and 1.4 mm in diameter. It is designed to be inserted into the upper or lower fornix of the eye where it is retained for an extended period of time, potentially up to several months depending on the drug and clinical applications. The drug is dispersed throughout the silicone rubber matrix. Thus, Ocufit SR® is a monolithic matrix system.

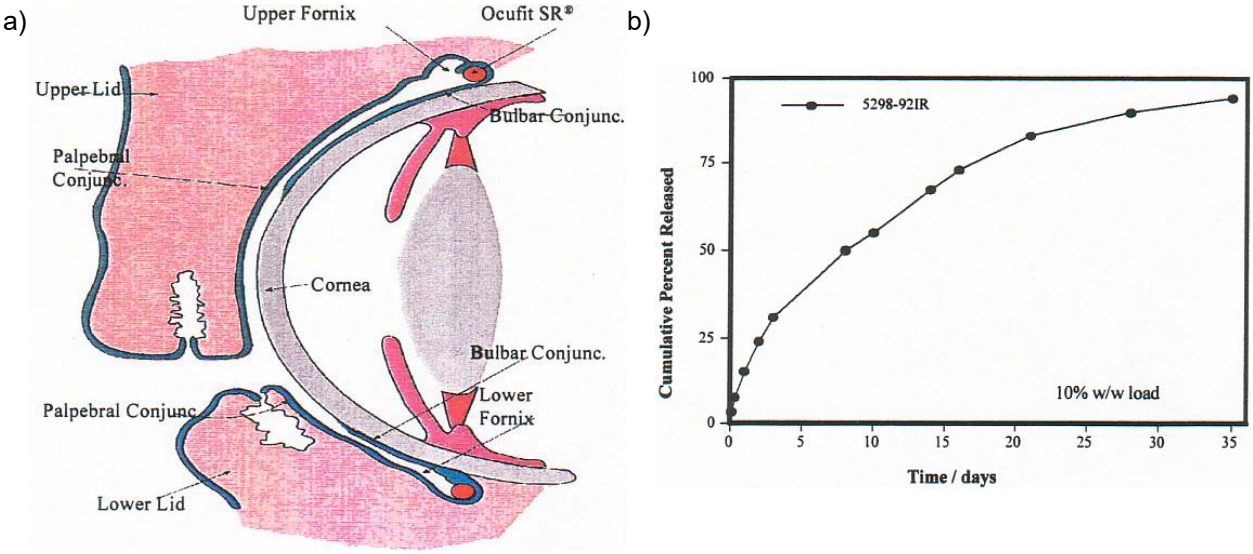


Figure 10.50 (a) Placement of the Ocufit SR® system. (b) *In-vitro* release rate of diclofenac from an Ocufit SR® system.

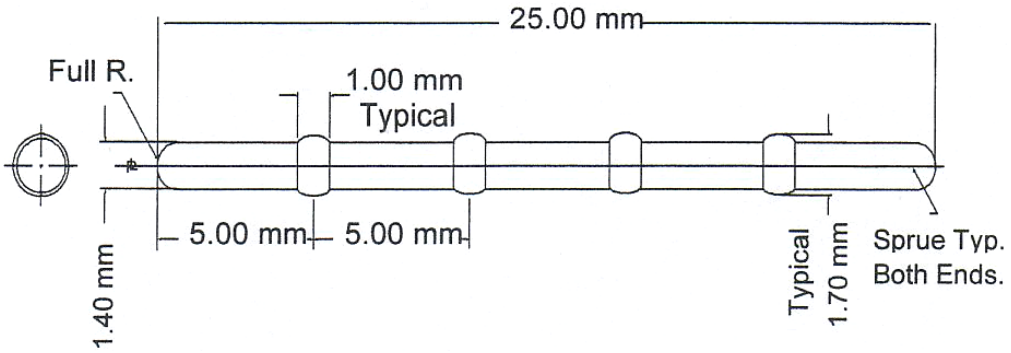


Figure 10.51 Schematic of the Ocufit SR® system.

QUESTIONS

1. The drug release profile from the Ocufit SR® is shown in Figure 10.50b. The release rate from the device is:
   (a) zero order
   (b) first order
   (c) second order
   (d) $t^{1/2}$ order
2. How can you control the rate of drug release from Ocufit SR®?
   (a) Vary the type of polymer matrix (*i.e.*, different types of silicone rubber or different polymers)
   (b) Add excipients to the matrix
   (c) Vary the amount of loaded drug
   (d) Apply coating later on the surface of the matrix

ANSWERS

1. (d)
2. (a–d)

5. DuraSite®

InSite Vision (Alameda, CA) is developing a DuraSite®-based formulation of an ophthalmic beta-blocker for the once-daily treatment of elevated intraocular pressure associated with glaucoma and ocular hypertension.

VII. PULMONARY CONTROLLED RELEASE DOSAGE FORMS

In the last quarter of the 20th century, pulmonary drug delivery has become a significant branch of pharmaceutical industry dedicated to provide effective therapies for treatment of asthma, chronic bronchitis, and cystic fibrosis. Inhalation of aerosolized drugs became a well-established modality for the drug delivery to the lung (Zeng, Martin, & Marriott, 1995). This is mainly due to its ability to deliver drugs conveniently to the site of action in the respiratory tract, while minimizing the risks of systemic toxicity (Gonda, 1999). Since the observation that anesthetic gases and other substances such as nicotine can be absorbed rapidly and effectively from

the respiratory tract, the pulmonary route has been explored for absorption of therapeutics that otherwise require invasive administration (*e.g.*, the majority of biotechnology products). The worldwide pulmonary drug-delivery market was $2.5 billion in 1993 and expected to reach $10 billion in 2000.

A. Advances in Inhalers

The inhaler technology has been improved dramatically to the point where accurate amount of dose can be delivered reproducibly. This ability is critically important for pulmonary delivery of protein drugs, such as insulin, which demands high levels of efficiency and reproducibility. This requires further extensive research into novel means of aerosol generation and delivery. Table 10.9 lists progressed made in inhalers. Chlorofluorocarbons (CFCs) are known to destroy ozone layer and a new generation of propellants are used. The spacer in inhalers improves actuator/breathing synchronization. The Rotahaler® dry powder inhaler has a filter that breaks particle aggregates into individual particles. Particle aggregation is a big problem in pulmonary delivery. The Spiros® dry powder inhaler (Dura Pharmaceuticals, Inc.) has an improved feature in that battery-driven propeller breaks particle aggregates. The power-driven propeller works better than a simple filter. Respimat® (Boehringer Ingelheim) has a nozzle and prefilter for improved function. The AERx™ system has an aerosol nozzle and the μm-scale holes on the membrane filter for delivery of power drugs. It is used for pain management and diabetes management. Pulmozyme® is the first genetically-engineered human protein approved by FDA via inhalation. No immune reaction to a foreign protein was observed. The time from cloning and FDA approval took only 5 years.

The further success in pulmonary delivery will depend on close cooperation between discovery research and formulation development, as well as in-depth understanding of aerosol generation and pulmonary physiology. A major tool for optimization (*i.e.*, drug aerosol deposition and disposition) of the pulmonary route of administration would be computer models simulating human anatomy and physiology.

Table 10.9 Advances in inhalers

Propellant-driven metered dose inhaler
Inhaler with a spacer
DeVilbiss glass jet nebulizer
Spinhaler (Fison) dry powder inhaler
Rotahaler dry powder inhaler
Spiros (Dura) dry powder inhaler
Pneumatic dry powder inhaler (Inhale)
Respimat (Boehringer-Ingelheim)
AERx™ (Aradigm Corp.)
Pulmozyme® (Dornase α) Inhalation Solution: For management of cystic fibrosis (including patients under age 5)

(Gonda, 1999) Gonda I (1999)

B. Advantages of Pulmonary Delivery

1. Local and Systemic Effect with Low Toxicity

Pulmonary delivery has been traditionally used for targeting the airways for treatment of asthma, bronchitis, cystic fibrosis. Pulmonary delivery can also be used for systematic treatment. One of the major advantages of pulmonary delivery is that the local toxicity associated with inhaled drugs for the treatment of respiratory tract disease is remarkably low. Pulmonary delivery results in near direct delivery to the target sites for many drugs. With the large surface area in the lungs, the pulmonary route provides a highly effective route of drug delivery.

2. Delivery of Peptide and Protein Drugs

Recent success in delivering insulin by inhalation would accelerate development of parenteral drugs as well as new chemical entities for pulmonary delivery. Protein delivery by pulmonary route relies on transcytosis. When tiny drug particles are inhaled deeply into the lung, they are taken up by small bubble-like invaginations of the deep-lung membrane growing at the surface of a lung cell. These invaginations eventually pinch off inside the cell to carrying a small sample of alveolar fluid and drug contained within that cell. The drug-containing membrane bubble moves across the cell to release its contents intact into the lung interstitium. Transcytosis allows crossing of particulate drugs through the thin tissue lining into the blood stream and then making their way to their intended destination.

Considering the difficulties associated with delivering protein drugs by

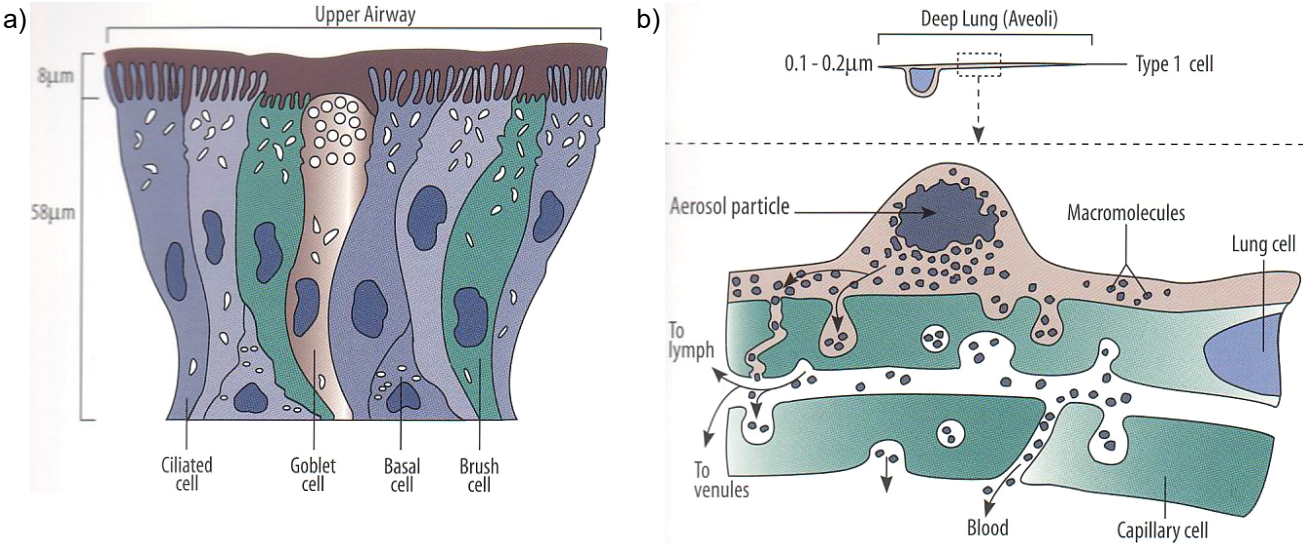


Figure 10.52 (a) The upper respiratory tract (the trachea and bronchial passages) is lined with a thick, ciliated, mucous-covered cell layer. Most inhaled drugs available today are deposited here or in the mouth with inefficient delivery methods where the major portion of each dose is moved to the throat and swallowed. (b) In adults, the alveolar tissue of the deep lung provides over 1,100 ft^2 of potential absorptive surface area, lined with a very thin, highly permeable, non-ciliated, mucous-free cell layer. The Inhale system efficiently delivers compounds to this tissue for subsequent systematic absorption.

oral route, one may conclude that pulmonary delivery may just be the answer for protein delivery by routes other than injection. In 1994, Genentech began marketing of the first aerosol-delivered protein, a recombinant form of the natural human enzyme deoxyribonuclease, which breaks down unwanted DNA that builds up in the lungs of patients suffering from cystic fibrosis. Many companies, such as Core Technologies (Kilmarnock, Scotland), focus on the delivery of small peptides with a molecular weight of about 100 using biodegradable microparticles.

C. PARTICLE AGGREGATION

The hope for many biotechnology companies producing respiratory drugs is that pulmonary delivery will emerge as the preferred route for some peptide and protein drugs such as insulin. Currently, pulmonary delivery costs more to deliver the same dose of an inhaled drug than it does to inject it. Furthermore, only a fraction (less than 5%) of inhaled drugs finds its way into the bloodstream as intended. The rest remains lodged in the delivery device or the patient's throat where it is not absorbed.

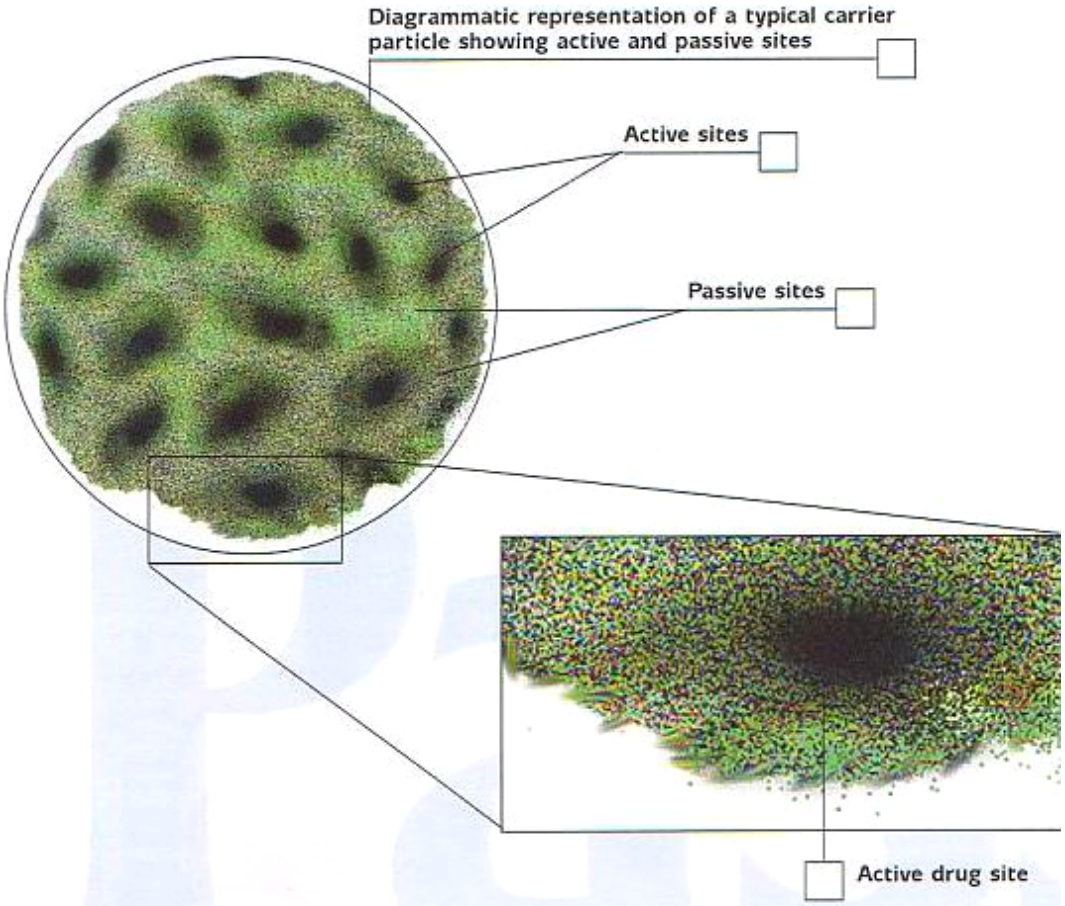
1. Aggregation in Propellants

In pulmonary delivery, the size and shape of particles are important. Mixing drug in a HFA propellant results in an high rate of aggregation. Aggregation of drug particles has been prevented by a number of approaches (*e.g.*, adding surfactants, coating drug particles, and other particle engineering). If drug particles are dispersed in a medium with the same density, particle aggregation can be reduced significantly. This is called homodispersion; no co-solvent is required in homodispersion.

2. Aggregation of Dry Particles

Drugs can be delivered in a dry powder form, and improved dose reproducibility depends on increased stability of the drug particles. For efficient inhalation of dry powders, small particles of sizes less than 5 μm are required, but the processing of such small particles is difficult. The small particles size is also prone to aggregation. Rotahaler® dry powder inhaler used dense microparticles, which tend to aggregate. Micronized particles with flat surfaces maximize cohesion leading to particle aggregation.

This problem can be partly overcome by attaching micronized forms of active ingredient to larger inert carrier particles or aggregates of the drug. Small particles lodge on the rough surface of bigger particles. Then, effective inhalation relies on efficient release of the active ingredient from the carrier or deaggregation of the drug aggregates so that the active ingredient passes down into the deep lung with the inspired air. This process is actually rather inefficient and less than 25% of the active drug inhaled is known to reach the deep lung. To make this process more efficient, Scherer DDS (a division of RP Scherer Corp.) uses the PassCaL™ formulation technology. The carrier particles are coated with a tertiary agent (such as L-leucine) to cover the sites on the carrier which would otherwise strongly adsorb the drug. Since the affinity of the drug to the carrier particle is reduced, the particle readily releases a consistent amount of



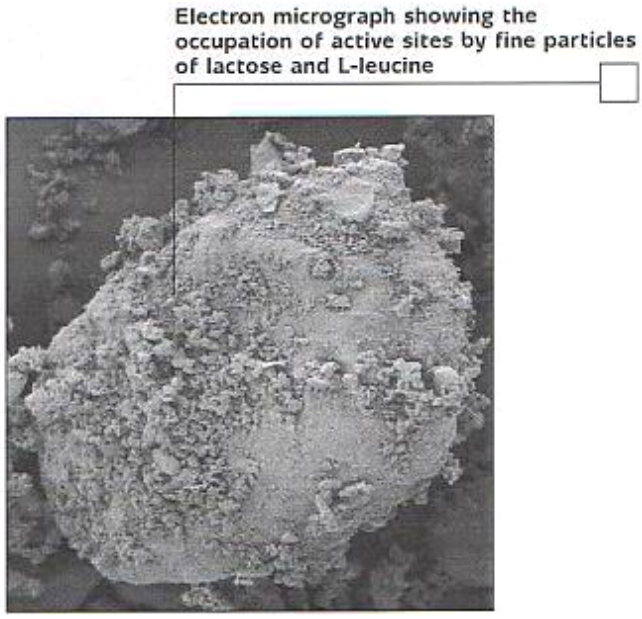


Figure 10.53 The PassCal™ formulation technology i , drug particles from the carrier particles by coating the carrier with a tertiary agent (the amino acid L-leucine). This covers the sites on the carrier that would otherwise strongly bind with the drug.

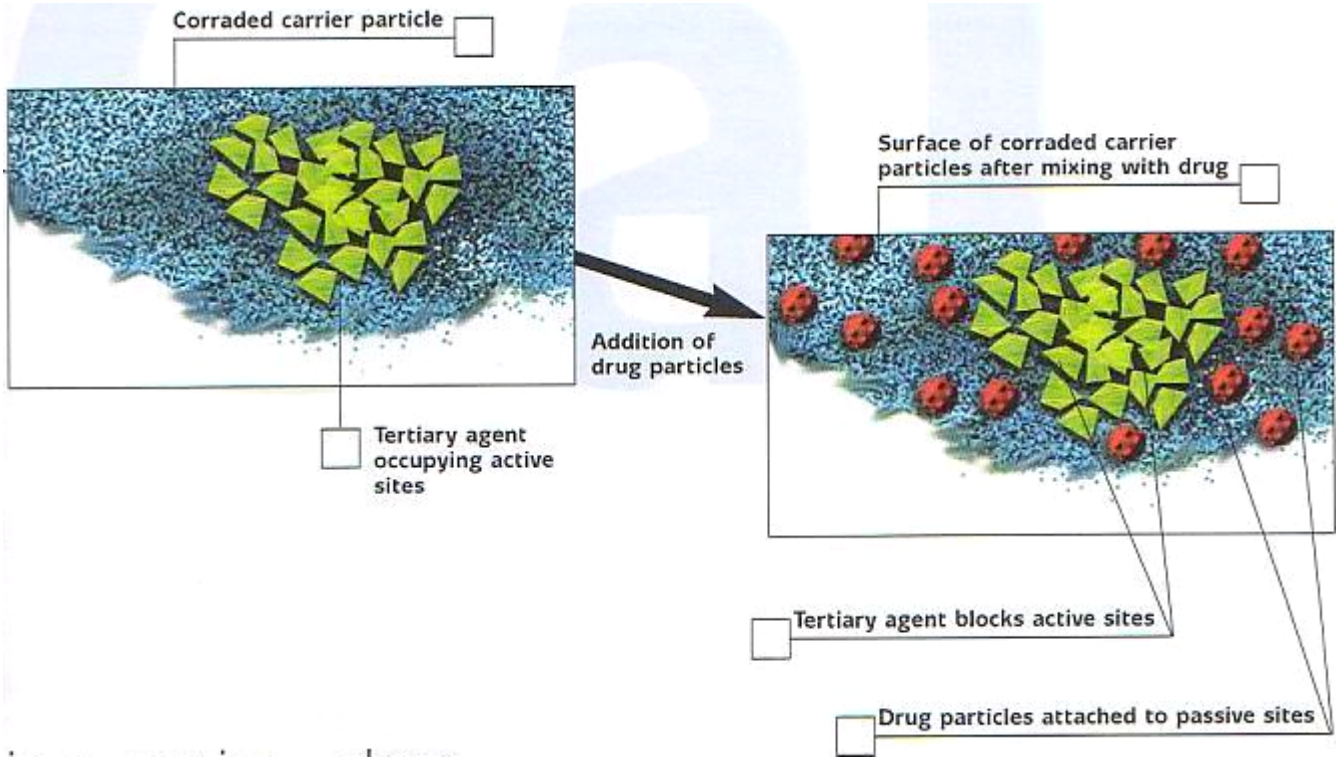


Figure 10.54 The reduction of site affinity is achieved by a novel one-step process known as corrasion. The result of corrasion is that each carrier particle takes up and readily releases a consistent amount of drug, improving the delivery of the inhaled active. PassCaL™ therefore increases the amount and reduces the variability of drug reaching the deep lung.

drug and improves the delivery of the inhaled drug. Elan Corp. (Dublin, Ireland) developed the PharmaZome™ technology. The active drug is uniformly embedded throughout insoluble polymer microparticles in a size of 50–125 μm. The drug is released by diffusion through the polymer matrix.

Alternatively, large, hollow particles can be used to reduce cohesion. Recently, hollow particles with greater size prepared by spray drying have been used. Pulmospheres® is an example. It is a hollow, porous, light, and dispensable particle. Lipid excipient coats the surface of particles as a monolayer for further stabilization. Pulmospheres® can be used in DPIs or MDIs. Other sponge-like particles and liposome-like particles can also be used. Large particles provide easier aerosolization and flow, and this makes them inhaled deep into the lungs. They are also less prone to phagocytosis.

Small sized particles are easy to aggregate, but big, porous particles of low density result in easy aerosolization and flowability, and are less prone to phagocytosis. They can be made by spray drying.

D. New Pulmonary Drug-Delivery Devices

A variety of controlled-release dosage forms have been prepared for drug delivery to the lung. Examples are liposomes, albumin microparticles,

poly(glycolic–co–lactic acid) microparticles, prodrugs, cyclodextrin complexes, and Technospheres® (which are microspherical particles formed by the protonation-driven self-assembly of a discrete, well-characterized small molecules developed by Pharmaceutical Discovery Corp. in Elmsford, NY). Liposome delivery systems have an advantage over others in that phospholipids used to make liposomes can be endogenous to the lung as surfactants. Drug particles can be delivered directly. Nicotrol® Inhaler allows a patient to puff on plastic mouthpiece containing nicotine cartridge. It delivers 4 mg of nicotine, which is about one-third of the blood level delivered by a cigarette.

There are a number of companies focusing on pulmonary drug-delivery systems. Most of these companies are focusing on the delivery of peptide and protein drugs using proprietary delivery systems (Pramik, 1997). The recent trend is to deliver drugs in the dry-powder form. The following examples are new devices developed for delivery dry-powder drugs.

1. Inhale Dry Powder Inhaler

Inhale Therapeutics, Inc. (San Carlos, CA) uses a slow inhalation technique which allows particles of 1–3 μm to enter the lung circulation. The highly soluble dry-powder aerosols are then quickly dissolved in the lung fluids. Currently, insulin for diabetes, calcitonin for osteoporosis, and interleukin-1 receptor for asthma are in clinical trial using the dry-powder inhaler system (Pramik, 1997). Inhale and its partner, Pfizer, Inc. (New York, NY), tested inhaled insulin to observe that the efficacy was equivalent to that of the injected drug (Pramik, 1998). The inhaled insulin was able to achieve the same excellent blood-glucose control that was traditionally obtained with a regimen of several daily insulin injections. The pulmonary delivery of insulin is expected to dramatically change diabetes treatment, particularly in patients who have been hesitant to use appropriate insulin therapy because of the discomfort and inconvenience of injections.

Inhale's pulmonary delivery system integrates four technologies.

1) Dry powder formulation: this allows room temperature stability.
2) Dry powder processing: particle size is less than 5 μm to reach the deep lung.
3) Individual packaging of the powders: this provides a strong moisture barrier, very precise dosing, and the ability to deliver blister-packed doses of different strengths, important for drugs like insulin.
4) The inhalation device: this uses a sonic velocity jet of air to break up the fine powders.

2. AERx® System

Aradigm Corp. (Hayward, CA) has the AERx® Pulmonary Drug-Delivery System that was used to produce the SmartMist™ Asthma Management System. Dry-powder inhalers are in general flow rate dependent (*i.e.*, the dosage depends on the patient's inspiration rate). Some patient may get a full dose while others do not. This problem can be corrected by using me-

AERx Ultra™ AERx Essence™ AERx Essence™ disposable

Figure 10.55 AERx® second-generation devices are in various stages of development from *in-vitro* optimization to human studies. The devices include a smaller and lighter version of the first-generation electro-mechanical platform, AERx Ultra™, and an all-mechanical version, AERx Essence™. AERx Essence also has been configured into a disposable product.

chanical energy to take the dose. AERx™ Pulmonary Drug-Delivery System is an example (see Figure 55).

3. Spiros® Drug-Delivery System

Dry-powder inhalers from Dura Pharmaceuticals (San Diego, CA) help to deliver to the lung both locally and systemically acting compounds, such as proteins and peptides. The Spiros® drug-delivery system is a dry-powder system that aerosolizes pharmaceuticals in dry-powder formulation for propellant-free delivery to the lungs and nasal passages. The inhaler contains a motor, breath-actuated switch, impeller, mouthpiece, and dosing chamber. The key to the system's performance is the application of electromechanical energy to generate a powder aerosol. The battery-powered motor spins the impeller, which makes the powdered drug into an aerosol. By inhaling through the Spiros® mouthpiece, the patient activates a flow switch, causing an impeller to rotate rapidly to disperse the drug. This action creates a cloud of aerosolized powdered drug for inhalation. The use of mechanical energy in the Spiros® system makes it independent on how much inspiratory force the patient can achieve. Flow-rate dependent dosing problem is minimized with this system. Another plus with the Spiros® and other dry-powdered inhalers is it requires no environment-damaging CFCs.

Dura Pharmaceuticals Inc. markets Ceclo CD®, an extended-release antibiotic for the treatment and maintenance of respiratory illness, developed by Eli Lilly and Co. Ceclo CD® uses the Spiros® drug delivery system

4. Turbuhaler®

Pulmicort Turbuhaler® (budesonide inhalation powder) for asthma control is from Astra. (Budesonide is a synthetic corticosteroid that helps fight inflammation). Corticosteroids are used to treat asthma because they reduce swelling and irritation in the walls of the small air passages and ease breathing problems. Turbuhaler® provides a correct dose each time by simply twisting the bottom grip. Patients can then inhale the dose of medication.

5. Rotacaps®

Ventolin Rotacaps® for Inhalation contain a dry-powder presentation of albuterol sulfate intended for oral inhalation only. The drug, in a hard gelatin capsule, is inhaled using a specially designed plastic device for inhaling powder called the Rotahaler®. This device, when turned or twisted, opens the capsule and facilitates dispersion of the drug into the air stream created when the patient inhales through the mouthpiece. This is an alternative inhalation form of albuterol to the metered-dose pressurized inhaler.

6. Diskus® inhaler

Serevent Diskus® inhaler by GlaxoWellcome delivers a controlled dose of salmeterol xinafoate inhalation powder. The drug is prearranged into individual doses, ensuring a consistent dose every time. Serevent Diskus® is a plastic device containing a strip of double-foil blisters containing a powder formulation of salmeterol xinafoate. The patient rotates the device, which prepares a dose to be released, and inhales. The arm sill of the device punctures a blister allowing the powder to enter the air stream created by the patient through the mouthpiece. Thus, the amount of drug actually delivered to the lungs is dependent on inspiratory flow of the patient. The inhaler was a finalist in the 1998 Medical Design Excellence Awards, which are sponsored by Canon Communications, LLC.

7. Schering-Plough's Dry-Powder Inhaler

Schering Plough Corp.'s (Madison, NJ) dry-powder inhaler delivers the drug using only the patient's breath, eliminating the need for propellants. The container counts the number of doses delivered and shows the patient how many are left. The system won a 1998 DuPont Gold Award for innovation in packaging technology. Schering Plough shared the honor with Courtesy Corp. (Buffalo Grove, IL), Glenn Beall Plastics (Gurnee, IL), and Huck and Studer Design Inc. (Gladstone, NJ).

VIII. VAGINAL AND INTRAUTERINE CONTROLLED-RELEASE DOSAGE FORMS

A. Vaginal Contraceptive Ring

Various drugs are known to effectively absorb through the vaginal mucosa. Contraceptive steroids have been administered through the vaginal route. In 1970 a vaginal contraceptive ring was developed using a silicone elastomer (Silastic™). The device is 55 mm in diameter × 9 mm thick and contains either 100 mg or 200 mg of medroxyprogesterone acetate. The contraceptive plateau levels were reached within 2–3 d and maintained throughout the 3-wk treatment period.

Although the progestin-releasing vaginal rings did not cause any significant adverse effect, the rings containing either medroxyprogesterone acetate or norgestrel quite often caused irregular breakthrough bleeding. The problem was largely avoided by delivering both progestin and estrogen simultaneously using a sandwich-type vaginal ring (see Figure 10.56).

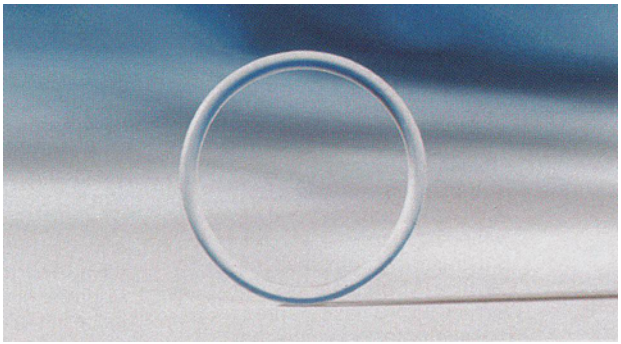


Figure 10.56 The NuvaRing® is a thin flexible plastic ring that women can flatten like a rubber band and insert once a month into the vagina. Moisture and body heat activate the release of the same progestin and estrogen found in low-dose birth-control pills (Hamilton & Bower, 2001).

B. INTRAUTERINE DEVICES (IUDS)

The development of intrauterine contraceptive devices (IUDs) began in the 1920s when the first generation of IUDs was constructed of silkworm gut and flexible metal wire. This early efforts led to IUDs of various shapes and sizes constructed from a variety of inert biocompatible polymeric materials (see Figure 10.57). IUDs became available in the 1960s as an alternative method of fertility control to women who experienced adverse reactions with oral contraceptive pills.

IUDs can be divided into non-medicated and medicated IUDs. The non-medicated IUDs currently available for intrauterine contraception consist of ring-shaped IUDs made of stainless steel and plastic IUDs fabricated from polyethylene or polypropylene. In the United States, only Lippes Loop® IUD (Ortho) is commercially available. Dalkon® shield and the Saf-T-Coil® are no longer available. The effectiveness of these non-medicated IUDs in preventing pregnancy depends primarily on their mechanical effect on the endometrial surface and thus, is proportional to the surface area of the device in direct contact with the endometrium. This makes the large IUDs more effective in preventing pregnancy than the small ones. Unfortunately, larger IUDs also cause more undesirable side effects such as irritation of the endometrium, endometrial compression, and myometrial distension, leading to increased uterine cramps, bleeding, and expulsion of the IUDS (Madan, 1985b). A new era of development for long-term intrauterine contraception was initiated with a T-shaped polyethylene device, with its small surface area and with significantly reduced side effects (see Figure 10.58).

Medicated IUDs deliver antifertility agents. Two classes of medicated IUDs are the copper-bearing IUD (*e.g.*, Cu-7®, GD Searle & Co.) and the progesterone-releasing IUD (*e.g.*, Progestasert®, Alza Corp.).

In the late 1960s, IUDs releasing an antifertility agent (such as progestin or metals like copper) were conceived. The Cu-7® IUD manufactured by GD Searle & Company was the first copper-bearing IUD approved by FDA for three-year intrauterine use. The Cu-7® made of polypropylene is shaped like a "7" and has 89 mg of copper wire winding

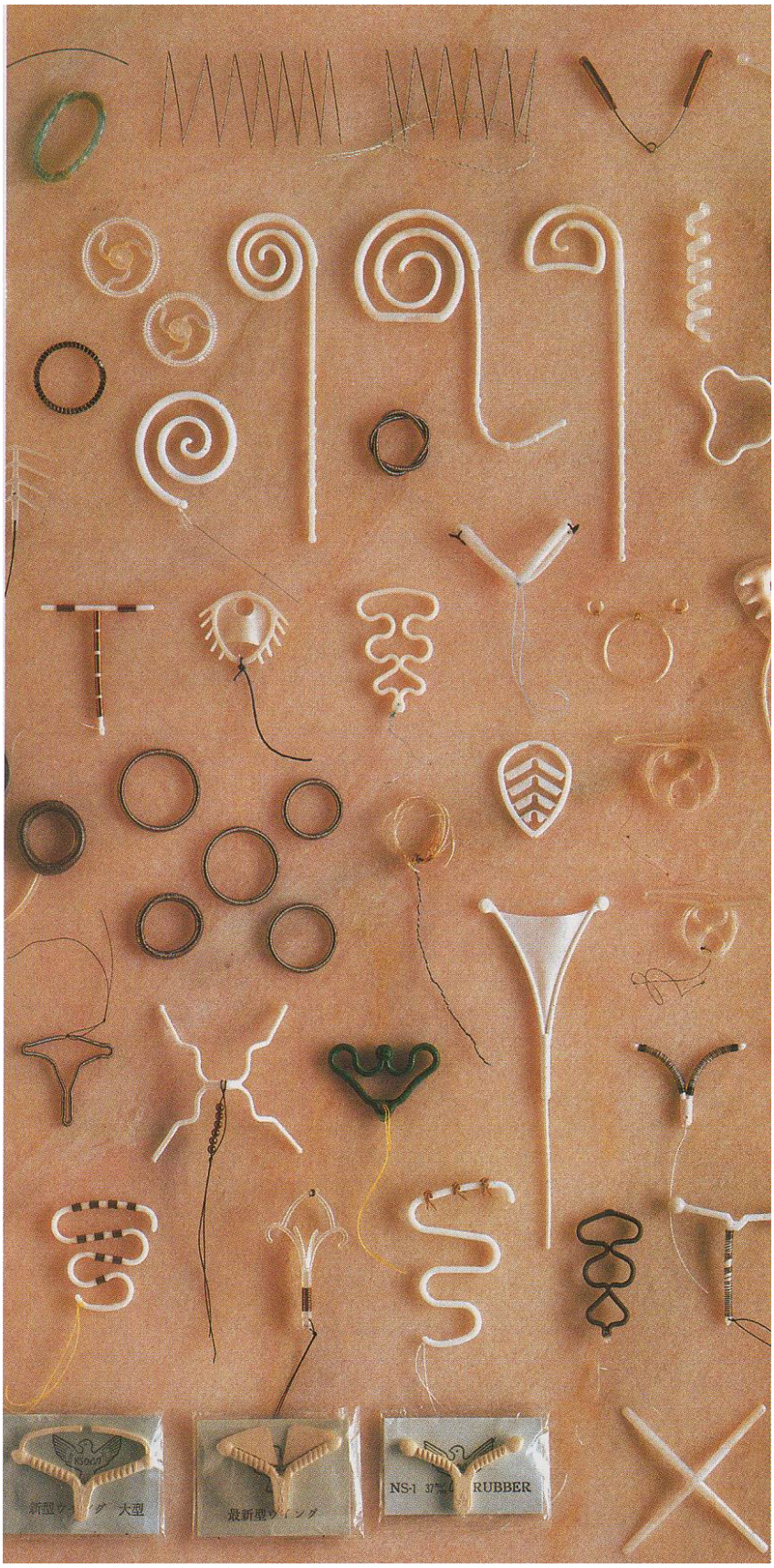


Figure 10.57 A display of the various shapes and sizes of IUDs constructed from a variety of inert biocompatible polymeric materials (Davidson, 2001).

around the vertical limb, providing approximately 200 mm^2 of exposed copper surface area. Another copper-bearing IUD marketed by GD Searle is Taturn-T®, a T-shaped polyethylene device containing 120 mg of copper wire winding around the vertical leg of the "T" and providing approximately 210 mm^2 of exposed copper surface area (Madan, 1985b).

Mirena® (levonorgestrel-releasing intrauterine system) is a unique form of long-acting birth control. It is a small, T-shaped frame made of soft, flexible plastic and is about the size of a quarter (see Figure 10.58). It is placed in the uterus (see Figure 10.59) by your health care professional during a routine office visit and continuously releases a very small amount of levonorgestrel (one of the hormones commonly found in the Pill). Mirena® prevents pregnancy for five full years or until removal.

The progesterone-releasing IUDs represent a new approach to steroidal contraception that localizes the effect of the active hormone to the uterus (*i.e.*, its effects are confined to the uterus). The first successful commercial intrauterine progesterone contraceptive system (Progestasert®) was introduced by Alza in January 1976. Progestasert® is a T-shaped unit constructed of ethylene–vinyl acetate copolymer containing 38 mg of proges-

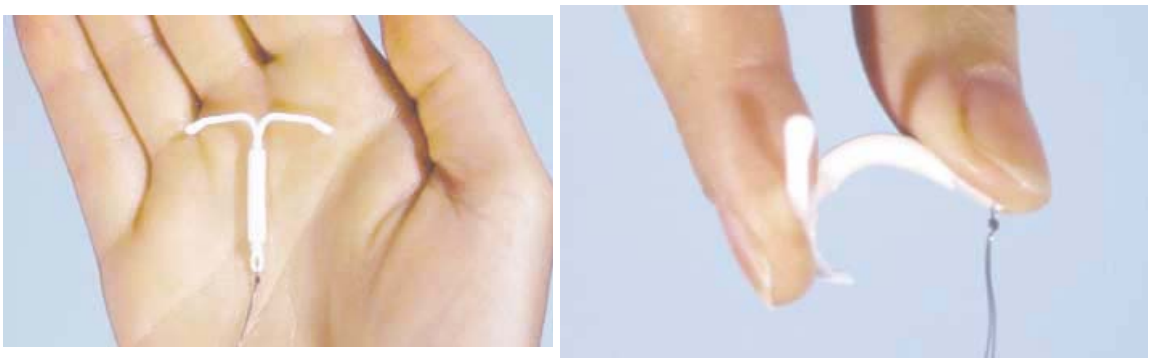


Figure 10.58 A pictures of the Mirena® IUD showing it's relative size and flexability.

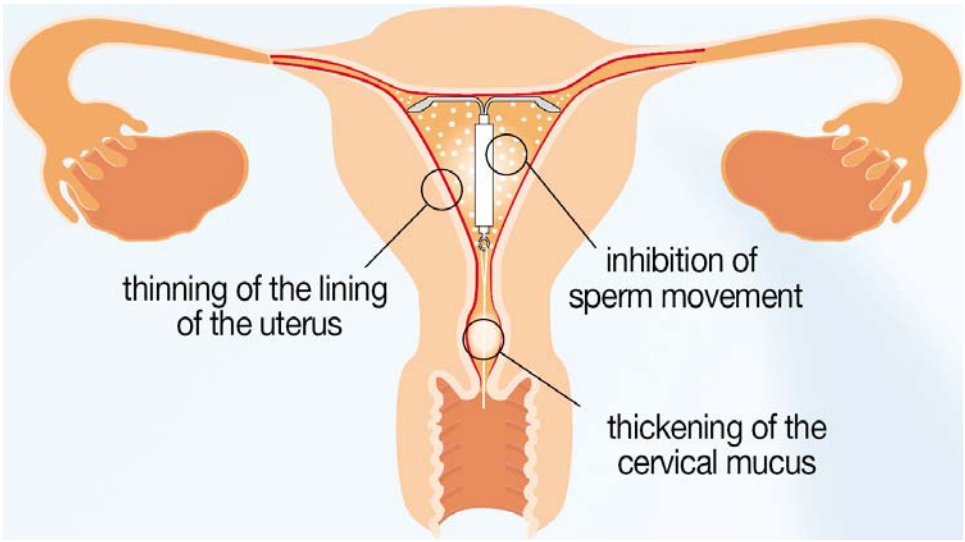


Figure 10.59 Illustration of the Mirena® IUD placement.

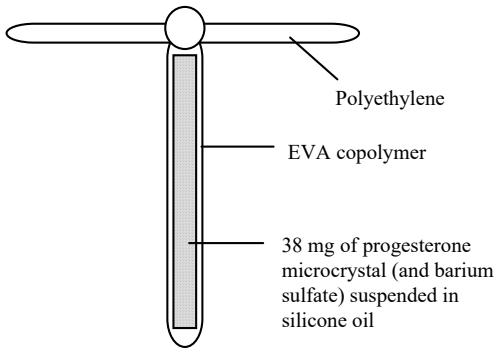


Figure 10.60 Cross section of the Progestasert® IUD.

terone. The system releases progesterone at an average rate of 65 μg/d for one year. The pregnancy rate was reduced to a minimum of 1.1% with the release of 65 μg/d. Further increase in the progesterone release rate did not reduce the pregnancy rate anymore (Madan, 1985b).

A cross section of the Progestasert® IUD and its composition are shown in Figure 10.60. The drug reservoir is a suspension of progesterone crystals in silicone medical fluid. The drug reservoir is encapsulated in the vertical limb of a T-shaped device walled by a nonporous membrane of EVA copolymer. The Progestasert® is made to deliver natural progesterone in the uterine cavity at a daily dosage rate of 65 μg/d to achieve contraception for 1 year.

C. CRINONE®

Crinone® is a sustained-release, vaginally delivered, natural progesterone product. It was developed by Columbia Laboratories, Inc., and marketed by Wyeth-Ayerst Laboratories. Crinone® uses a bioadhesive delivery system, poly(acrylic acid), to deliver progesterone directly to the uterus.

D. REPLENS®

Replens® is a over-the-counter product using bioadhesive polymer, poly(acrylic acid) developed by Columbia Laboratories Inc. It replenishes vaginal moisture on a sustained basis and relieves the discomfort associated with vaginal dryness. It is now marketed by Warner-Lambert Co.

E. FEMSTAT-1®

Femstat-1® is a cream for vaginal fungal infections. It uses the Site Release® controlled-release technology from KV Pharmaceutical Inc. (St. Louis, MO) for liquids, creams, and semi-liquids. It is marketed by Roche Laboratories.

F. TODAY SPONGE®

The Today Sponge® is a contraceptive for women manufactured by Whitehall-Robins Healthcare. The Today Sponge® (see Figure 10.61) is only one of many OTC contraceptives for women that are on the market,

Figure 10.61 The Today Sponge®.

including a female condom and spermicides. Available prescription contraceptives for women include IUD, injection, implant, diaphragm and cervical cap with spermicide, and various birth control pills (McLearn, 1995).

The firm stopped production in March, 1994 after the FDA's inspection disclosed bacterial contamination of the water used to make the Today Sponge®. After weighing the cost of modifications that would be necessary to bring the plant up to acceptable manufacturing standards, as well as the likely loss of the Today Sponge®'s market share by the time the upgrading would be completed, the firm decided to stop making the contraceptive (McLearn, 1995). The Today Sponge®, however, is now back.

G. HYCORE-V™

The Hycore ™ (Core Technologies Ltd., UK) delivery system is based on hydrogels that absorb water and swell without losing its physical form. The incorporated drug is released as the hydrogel absorbs water to swell. The drug release rate can be controlled by adjusting the crosslinking density (influencing the extent of swelling) and the shape (affecting the surface area). The drug delivery can be controlled over a wide range of time period ranging from hours to days. Hycore-V™ is a hydrogel pessary for local drug delivery in the vagina. Hycore-R™ is a rectal delivery system for systemic drug delivery.

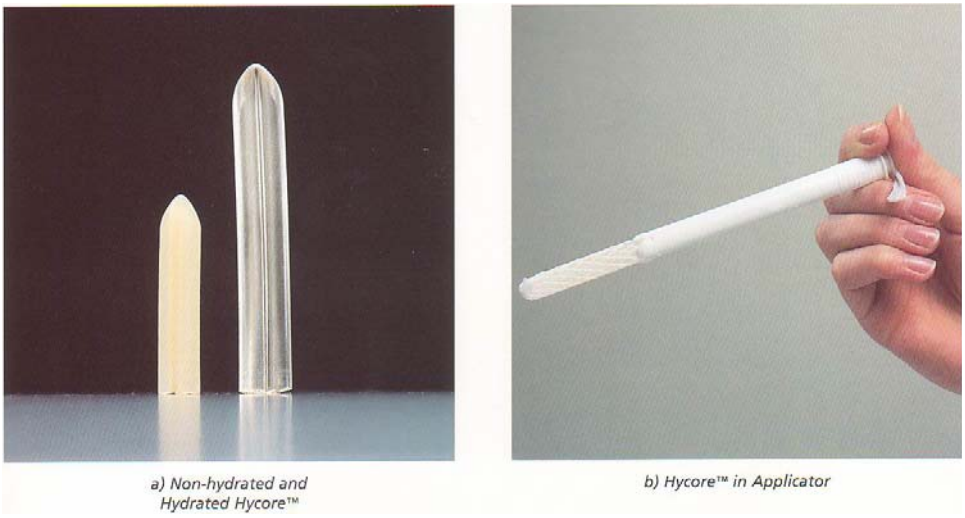


Figure 10.62 (a) Hycore™ pessary in the non-hydrated and hydrated states. (b) Hycore™ applicator.

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