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Potential Developments and New Approaches in Oral Controlled-Release Drug Delivery Systems

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Introduction

The terms, controlled-release and sustained-release are not new to many of us working in various disciplines of pharmaceutical research and development. Approximately 20 years ago, FDA had already published regulatory requirements for Controlled Release Products. Unfortunately, there has been a proliferation of Controlled-Release Dosage Forms on the marketplace that may have little rationale and provide no advantages over the same drugs in Conventional Dosage Forms. In the last decades there has also been an increase in the (possibly unwarranted) use of controlled-release labeling claims. (1)

Controlled-release drug administration means not only prolonged duration of drug delivery, as in sustained-release and pro-

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longed-release, but also implies predictability and reproducibility of drug release kinetics. (2)

For the oral controlled administration of drugs, several R & D activities have shown encouraging signs of progress in the development of programmable controlled-release drug products as well as in the search of new approaches to overcome the potential problems associated with oral drug administration. These potential developments and new approaches will be reviewed in this presentation.

In the exploration of oral controlled drug administration, one encounters 3 areas of potential challenge:

1) Drug delivery system - Development of a viable drug delivery system which is capable of administering a therapeutic agent at a programmed rate for a duration required for an optimal treatment.

2) Gastrointestinal transit time - Prolongation of the gastrointestinal residence time, so the drug delivery system developed can reside at the vicinity of absorption site for sufficient long period of time to deliver all the drug loading dose.

3) Hepatic first-pass elimination - If the drug is subjected to an extensive hepatic "first-pass" elimination, preventive measures should be developed to minimize the extent of hepatic "first-pass" metabolism.

It is the intention of this lecture to review various potential developments and new approaches recently introduced to meet these challenges.

Development of Novel Drug Delivery Systems for Oral Controlled Drug Administration

Review of literature has revealed the recent development of a number of novel drug delivery systems which could be utilized for the controlled administration of drugs in the alimentary canal. These potential developments can be outlined and discussed as follows:

1. Osmotic pressure-controlled drug delivery systems

   It is fabricated by coating a core reservoir of an osmotically active drug, e.g., KCl, or of a combination of an osmotically inactive drug with an osmotically active salt, e.g., NaCl, by a biocompatible polymer e.g., cellulose acetate, to form a semipermeable, shape-retaining coating (Fig. 1). A delivery orifice with a controlled diameter is drilled by a laser beam through the coating membrane for the release of drug solutes (U.S. Patent #4,036,227).

   This coating membrane is rigid and capable of maintaining the structural integrity of the drug delivery system during the course of drug release. It is permeable to the influx of gastrointestinal fluid, but is impermeable to drug solutes. When in use, the gastrointestinal fluid, which is continuously imbibed through the

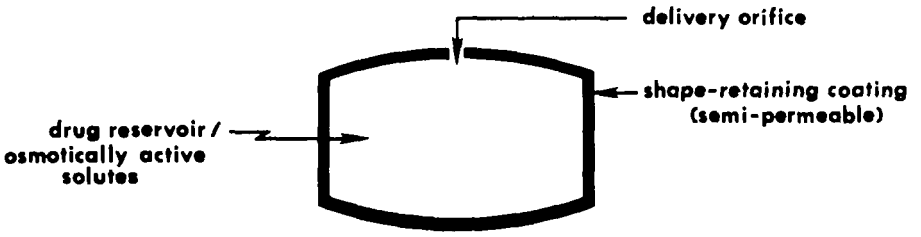


Fig. 1: Osmotic Pressure-controlled Drug Delivery System (US patent #4,036,227)

semipermeable membrane into the drug reservoir compartment, quickly dissolves the osmotically active salt and creates an osmotic pressure gradient across the membrane. Under this osmotic pressure gradient, the drug solutes are continuously dispensed through the delivery orifice, over a prolonged period of time, at a rate defined by the following relationship:

$$\left(\frac{Q}{t}\right)_z = \frac{P_w A_m}{\delta_m} \left[\pi_s - \pi_e\right] S_D$$

Where P_w, A_m and δ_m are, respectively, the water permeability, the surface area and the thickness of the semipermeable membrane; π_s is the osmotic pressure in the saturated solution of osmotically active salt in the system; π_e is the osmotic pressure in the gastrointestinal tract; and S_D is the solubility of the drug. (3)

In principle, this type of drug delivery system dispenses the drug solutes continuously at a zero-order rate until the concentration of the osmotically active salt in the system drops down to the level below the

saturation solubility. Then, a non-zero-order release pattern is resulted at a rate described by:

$$\frac{dQ}{dt} = \frac{(Q/t)_z}{\left[1 + \frac{(Q/t)_z}{S_D \cdot V_t}(t - t_z)\right]^2}$$

where $(Q/t)_z$ is the rate of zero-order drug release; V_t is the total volume inside the system; t_z is the total time at which the system delivers the drug at zero-order rate; and t is the total residence time.

The thickness of coating membrane affects the rate and the duration of zero-order release of drug from the osmotic pressure-controlled drug delivery systems (Fig. 2).

The external surface of the semipermeable membrane can be further coated with a layer of bioerodible polymer, e.g., enteric coating, to regulate the availability of gastrointestinal fluid for permeation through the semipermeable membrane (U.S. Patent #4,096,238).

The coating membrane of the delivery system can also be constructed from a laminate of two or more semipermeable membranes with differential permeability (U.S. Patent #4,058,122), or a laminate of a semipermeable layer and a microporous layer (GB Patent #1,556,149).

The osmotic pressure-controlled drug delivery system can be further modified to constitute 2 compart-

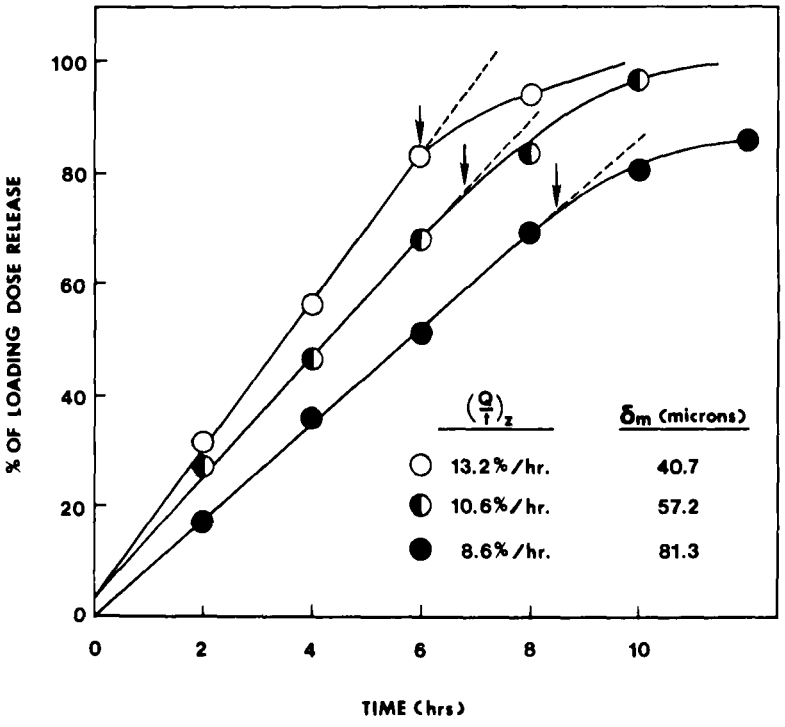


Fig. 2: Effect of Coating Membrane Thickness on the Rate and Duration of Zero-order Release of Indomethacin from Osmotic Pressure-controlled Drug Delivery System

ments separated by a movable partition (Fig. 3). The osmotically-active compartment imbibes liquid from the gastrointestinal tract to create an osmotic pressure on the partition, which, in turn, moves to force the drug reservoir compartment to reduce its volume and to release the drug solutes through the delivery orifice (GB Patent #1,551,898).

The potential application of osmotic pressure-controlled drug delivery systems for oral controlled administration of drugs is demonstrated by the development of "Osmosin" tablet by Alza for Merck. The development and

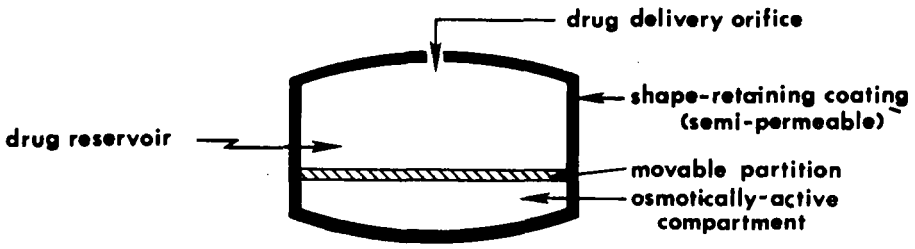


Fig. 3: Osmotic Pressure-controlled Drug Delivery System (GB patent #1,551,898)

evaluation of "Osmosin" tablet will be discussed in detail by Dr. Theeuwes in his lecture.

2. Hydrodynamic pressure-controlled drug delivery systems

In addition to the osmotic pressure we have just discussed, hydrodynamic pressure may also be utilized as the energy source for controlling the release of therapeutic agents.

A hydrodynamic pressure-controlled drug delivery system can be fabricated by enclosing a collapsible drug compartment inside a rigid shape-retaining housing (Fig. 4). The space in-between the drug compartment and the external housing contains a laminate of a layer of absorbent and a layer of swellable, hydrophilic crosslinked polymer, e.g., polyhydroxy alkyl methacrylate, which imbibes the gastrointestinal fluid through the annular openings in the lower end of the housing. The imbibition casues the laminate to expand and to generate a hydrodynamic pressure in the system, which forces the drug compartment to collapse and to deliver the liquid drug formulation through the delivery orifice (U.S. Patent #4,180,073).

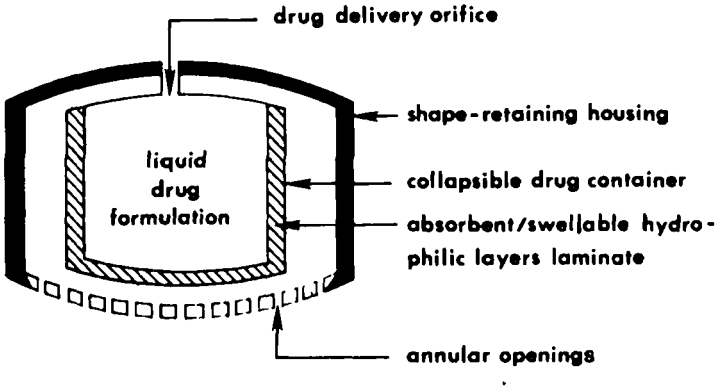


Fig. 4: Hydrodynamic Pressure-controlled Drug Delivery System (US patent 4,180,073)

3. Membrane diffusion-controlled drug delivery systems

Membrane diffusion process has been successfully applied in the development of controlled release drug delivery systems for transdermal controlled administration of nitroglycerin (Transderm-Nitro system), and of scopolamine (Transderm-Scop system) through the intact skin. These membrane diffusion-controlled drug delivery systems are known to use a prefabricated microporous membrane to meter the release of therapeutic agents.

Membrane diffusion process has also been utilized in the development of oral controlled-release drug delivery systems in which the microporous membranes are produced in the gastrointestinal tract directly from a non-porous polymer coating. Several potential developments, which have been proven feasible, are outlines as follows:

1) Microporous membrane-coated tablets

It is prepared by first compressing aqueous soluble drug particles into a core tablet with

appropriate pharmaceutical excipients and then coating the tablet with a layer of non-GI-eroding polymer, e.g., the copolymer of vinyl chloride and vinyl acetate. The polymer coating contains a small amount of water-soluble pore-forming inorganic substances, e.g., magnesium lauryl sulfate, to create porosity when the tablet is in contact with gastrointestinal fluid (Fig. 5). The porosity and rigidity of the polymer coating can be varied to give a slow or fast release at constant rates (NL Patent #7,313,696).

2) Solubility membrane-controlled solid dosage form

It is also prepared by first compressing aqueous soluble drug particles into a core tablet with appropriate pharmaceutical excipients and then coating the tablet with a layer of thermoplastic polymer, e.g., polyvinyl chloride. The polymer coating contains at least 80% of plasticizer, e.g., dioctyl phthalate, to create a solubility membrane in the gastrointestinal tract (Fig. 6). The rate of drug release can be controlled and predetermined by regulating the concentration of plasticizer in the polymer coating (BE Patent #814,491).

3) Enteric controlled-release tablets

The tablet, which is designed to release a drug labile to gastric fluid only in the intestine at a controlled rate, is prepared by coating a core tablet with a combination of intestinal fluid-insoluble poly-

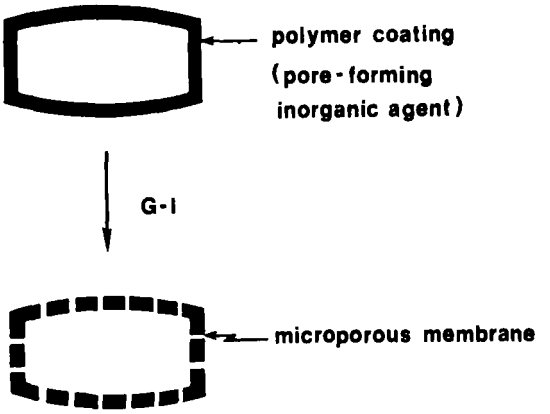


Fig. 5: Microporous Membrane-coated Tablet
(NL patent #7,313,696)

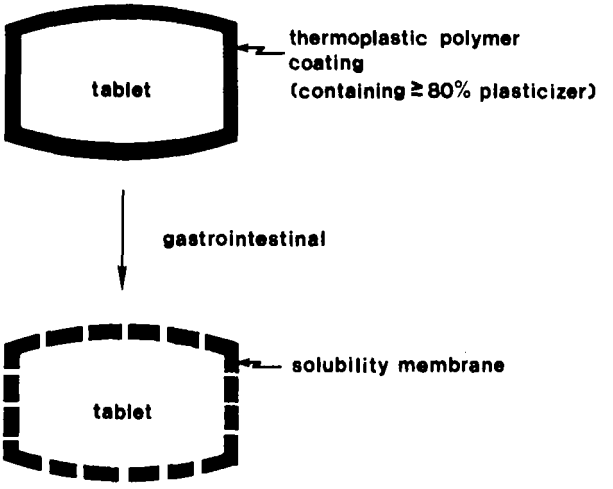


Fig. 6: Solubility Membrane-controlled Solid Dosage Form
(BE patent #814,491)

mer, e.g., ethyl cellulose, and intestinal fluid-soluble polymer, e.g., hydroxymethyl cellulose phthalate (Fig. 7).

In the intestinal tract, hydroxymethyl cellulose phthalate component is dissolved away by the intestinal fluid, leaving a microporous emebrane of ethyl

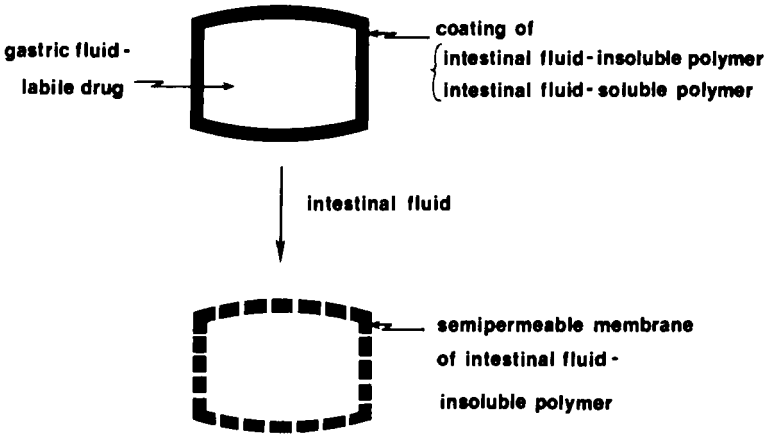


Fig. 7: Enteric Controlled-release Tablet (J patent #8-0,018,694)

cellulose, which renders a controlled release of drug in the intestine (J Patent #8-0,018,694).

4) Multi-laminated sustained-release tablets

The tablet is fabricated by first dispersing a loading dose of drug in layers of water-soluble carboxymethyl cellulose (CMC), sandwiching the drug-loaded CMC layers in-between layers of crosslinked carboxymethyl cellulose, which is water insoluble, but water swellable, and then compressing these layers under 13,000 p.s.i.g. pressure to form a multi-laminated tablet, which is then coated with a suitable polymer coating material (Fig. 8).

In the gastrointestinal tract, the crosslinked CMC layers become swollen and gelantinous and create a colloid gel barrier, which controls the release of drug from the CMC layers (U.S. Patene #4,180,558).

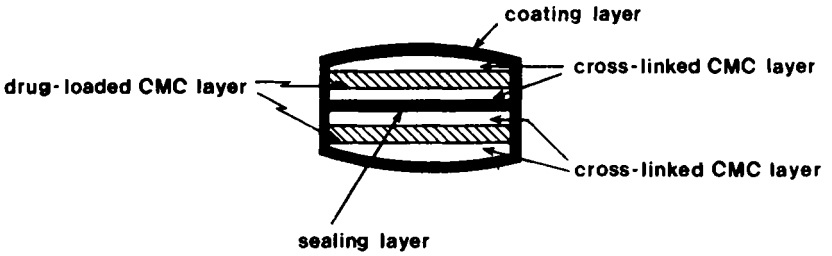


Fig. 8: Multi-laminated Substained release Tablet (US patent #4,180,558)

5) pH-independent controlled-release granules

The granules are designed for the oral controlled release of acidic or basic drugs at a rate which is independent of the variation in pH conditions along the gastrointestinal tract (Fig. 9).

They are prepared by blending an acidic or basic drug with one or more buffering agents, e.g., primary, secondary or tertiary salt of citric acid, granulating with appropriate pharmaceutical excipients to form small granules, and then coating the granules with gastrointestinal fluid-permeable film-forming polymer, e.g., cellulose derivatives.

The polymer coating acts as a permeation-controlling membrane, so that when the gastrointestinal fluid passes through the membrane, the buffering agents adjust the fluid to an appropriate constant pH, at which the drug dissolves and permeates through the membrane at a constant rate regardless of the location in the alimentary canal (DS Patent # 2,414, 868; BE Patent #812,909; SU Patent #665,778).

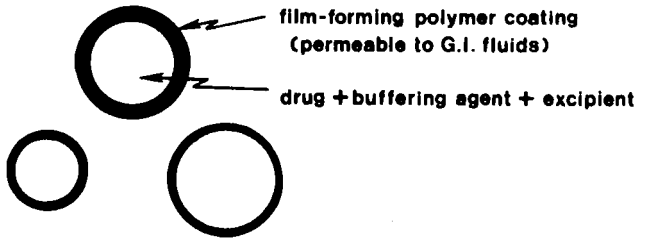


Fig. 9: pH-independent Controlled Release Granules (DS patent #2,414,868) (BE patent #812,909) (SU patent #665,778)

6) Polymer-coated Drug-Resin preparation

This preparation is designed to provide a controlled release of a therapeutic agent at a rate which is independent of any variation in pH conditions, enzymatic activities, and contents of the gastrointestinal tract (Fig. 10).

It is prepared by first adsorbing an ionizable drug onto the ion-exchange resin granules, such as codeine base and Amberlite (RTM)IRP-69, and then, after filtration from the alcoholic media, coating the drug resin complex granules with a water-permeable polymer, e.g., a modified copolymer of polyacrylic-methacrylic ester, and then spray-drying the coated granules to produce the polymer-coated drug-resin preparation. This approach has been utilized in several patentable developments (U.S. Patent #3,138,525; 3,499,960; 3,594,470; BE Patent #729, 827; DT Patent #2,246,037).

Further improvement of this ion-exchange type drug delivery system is the development of the

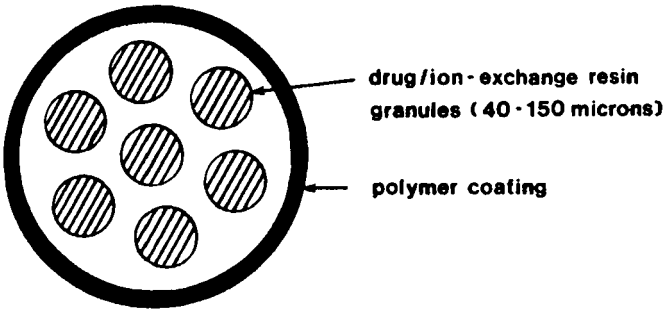


Fig. 10: Polymer-coated Drug-Resin Preparation (DT patent #2,246,037)

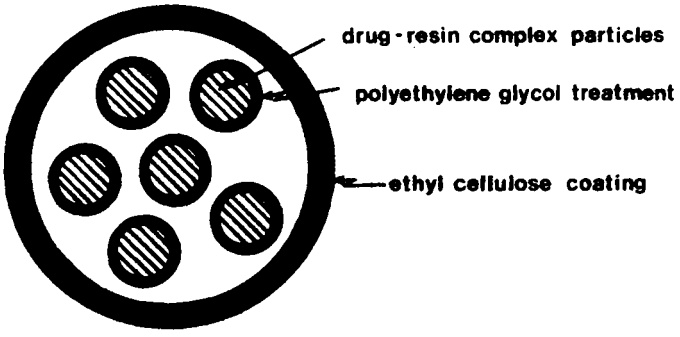


Fig. 11: Polymer-coated Drug-Resin Dispersion (US patent #4,221,778)

Pennkinetic system by Pennwalt Corporation (Fig. 11). In this system, the drug-resin complex granules are further treated with an impregnating agent, e.g., polyethylene glycol 4000, to retard the rate of swelling in the water and then coated, by air suspension technique, with a water-permeable polymer membrane, e.g., ethyl cellulose, to act as a rate-limiting barrier to control the release of drug from the system.

It is known that the ionic strength of the gastrointestinal fluids is relatively constant. In

the GI tract, ions diffuse through the ethyl cellulose membrane and react with the drug resin complex to release drug solutes (Fig. 12).

i. For cationic drug:

Proton will activate the release of cationic drug from the drug-resin complex.

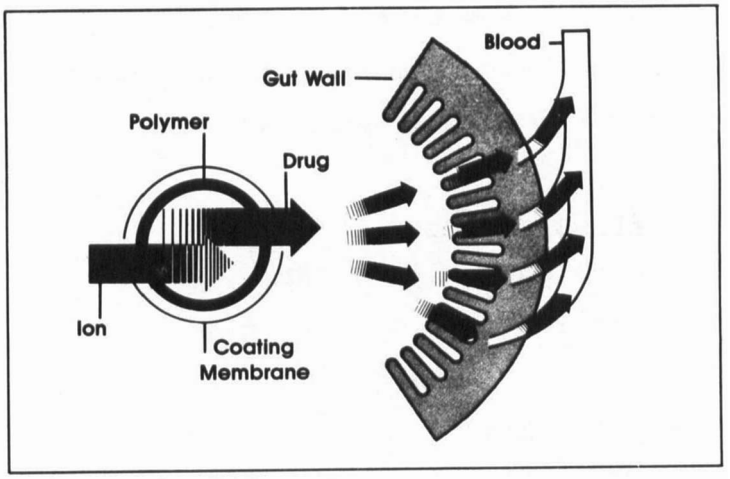
ii. For anionic drug

The chloride ion will activate the release of anionic drug from the drug-resin complex.

The free drug solutes then diffuse through the coating membrane into the gastrointestinal fluids for absorption.

Advantages of this system are that: (i) The rate of drug release is not dependent upon the pH conditions, enzyme activities, temperature and volume of the GI tract, (ii) The system is administered in the form of a large number of particles which may eliminate the effect of gastric emptying, and (iii) It can be formulated as a stable liquid suspension.

By combining different ratios of coated and uncoated granules in the formulation, a range of dissolution profiles and blood levels can be achieved (Fig. 13). Uncoated granules serve as the initial release dose and coated granules serve as the slow-release maintenance dose.



$$H^{\oplus} + \text{Resin} - SO_3^{\ominus}\ \ \text{Drug}^{\oplus} \rightleftharpoons \text{Resin} - SO_3^{\ominus}\ H^{\oplus} + \text{Drug}^{\oplus}$$

$$Cl^{\ominus} + \text{Resin} - \left[N(CH_3)_3^{\oplus}\right]\ \text{Drug}^{\ominus} \rightleftharpoons \text{Resin}\ \left[N(CH_3)_3^{\oplus}\right]\ Cl^{\ominus} + \text{Drug}^{\ominus}$$

Figure 12

7) Thixotropic bilayer tablets

Each layer of the bilayer tablet is prepared by dissolving or dispersing, if not soluble, the drug(s) in a gel made from different levels of Thixcin R (hydroxyglycerol ester of a monobasic $C_{16} \sim C_{18}$ fatty acid) in a solvent, e.g., ethanol. Solvent is then evaporated to give a drug dispersing matrix, which can be screened, granulated and compressed into a core tablet (Fig. 14). By varying the ratio of drug to Thixcin R, the rate of drug release can be controlled.

In the gastrointestinal tract, Thixcin R absorbs water and becomes a semi-rigid mass. It

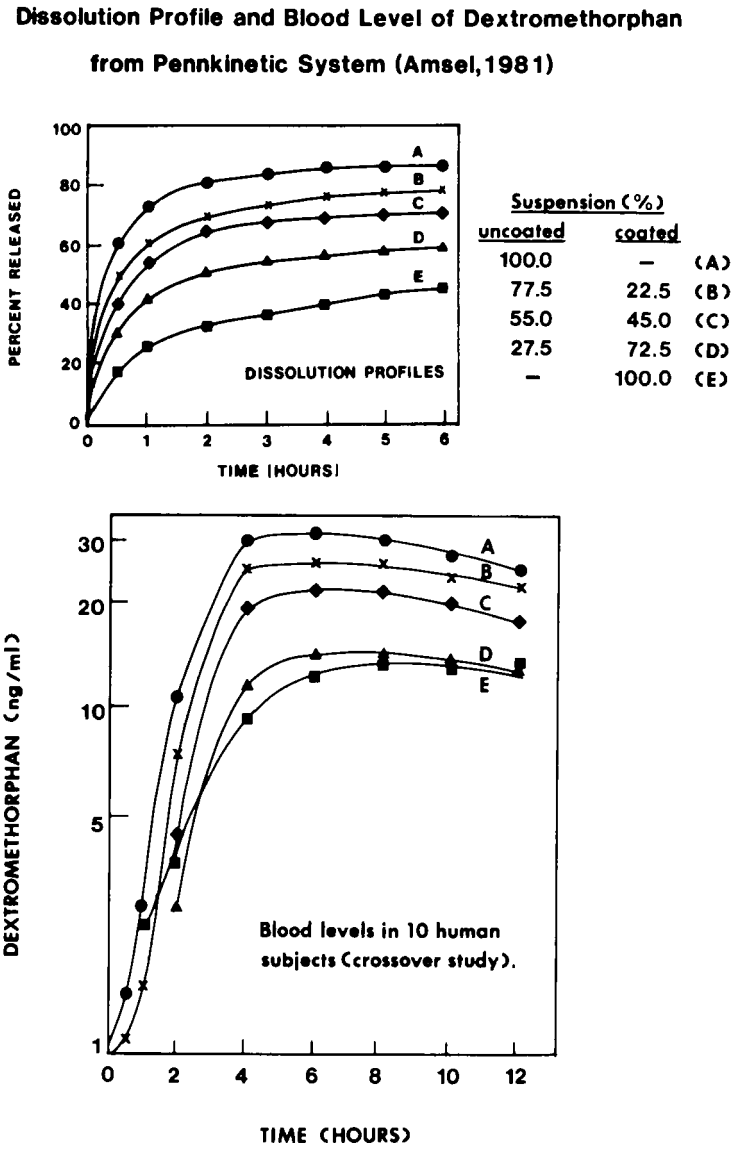


Fig. 13: Dissolution Profile and Blood Level of Dextromethorphan from Pennkinetic System (Amsel, 1981)

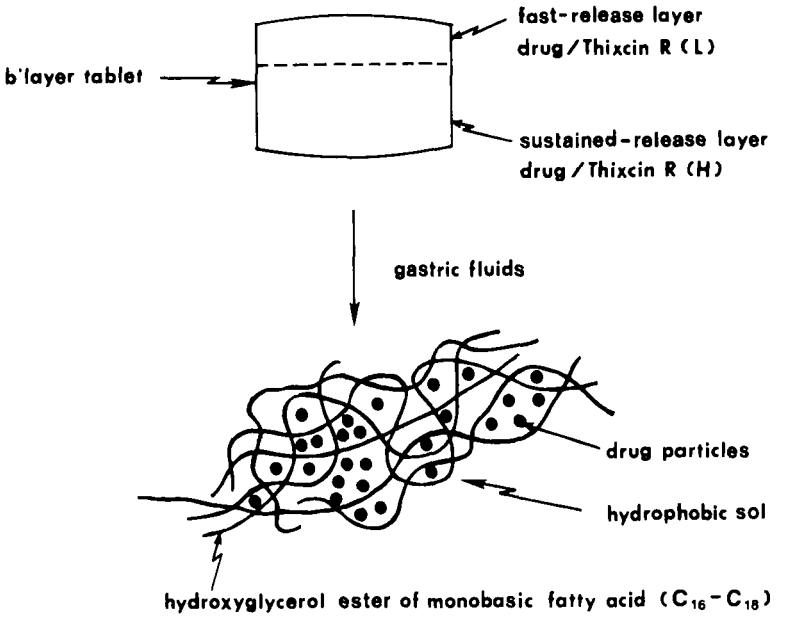


Fig. 14: Thixotropic Bilayer Tablet
(US patent #3,136,695)

behaves as a hydrophobic sol in which thread-like aggregates interlock and disperse throughout the liquid medium.

Prolongation of Gastrointestinal Transit Time

All of the controlled-release drug delivery systems discussed so far will have only limited utilization in the oral controlled administration of drugs if the systems can not remain in the vicinity of the absorption site for the lifetime of the drug delivery.

The transit time from the mouth to the anus varies from one person to another. It also depends upon the physical properties of the object ingested and the physiological

conditions of the alimentary canal. A study conducted by Hinton and his associates [4] indicated that the alimentary canal transit time for an indigestible object can vary from 8 to 62 hours. However, 50% of the human subjects were found to excrete the object within 24 hours (Fig. 15).

Therefore, the majority of the controlled - or sustained-release drug products designed for oral drug administration have a limited residence time in the vicinity of absorption sites, 2-3 hrs. as pointed out by Dr. Hofmann. So, most of the long acting drug products require a dosing schedule of twice a day.

Several approaches have recently been developed to extend the gastrointestinal transit time by sustaining the residence time of the drug delivery systems in the stomach.

1. Intragastric Floating Tablets

On contact with gastric fluid, the intragastric floating tablet forms a water-impermeable colloid gel barrier around its surface and maintains a bulk density of less than one. So, it remains buoyant in the gastric fluid inside the stomach until all the drug loading dose has been released (Fig. 16).

The tablet formulation is prepared by simply granulating a homogeneous mixture of drug, pharmaceutical excipients and 20-75% w/w of one or more hydrocolloids, e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxprypylmethyl cellulose and sodium carboxymethyl cellulose. These

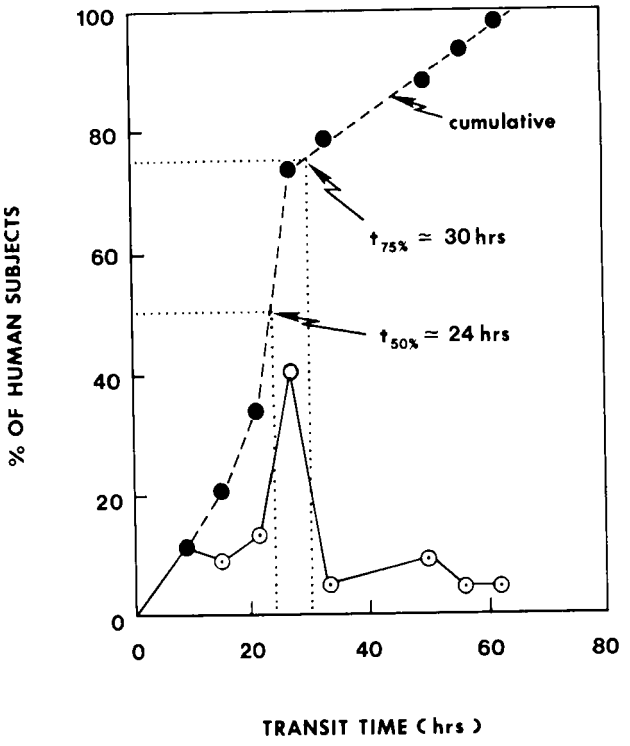


Fig. 15: Alimentary Canal Transit Time for an Excreting Marker in Humans (Hinton et al, 1969)

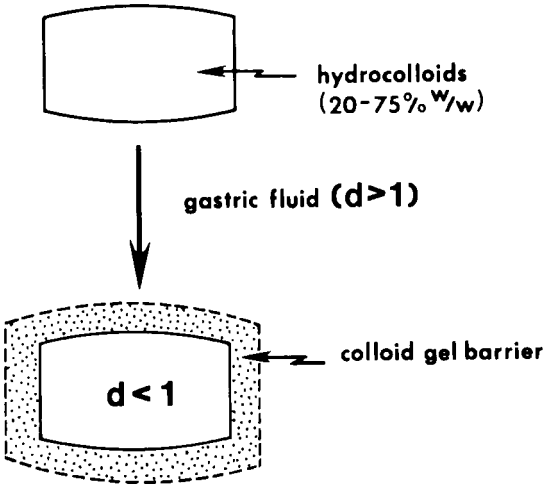


Fig. 16: Intragastric Floating Tablet (US patent #4,167,558)

granules are then compressed to a hardness of 5-6 scu. (U.S. Patent #4,167,558).

A Bilayer tablet can also be prepared to contain one immediate release layer and one sustained release layer (Fig. 17). After the initial dose is released from the immediate release layer, the sustained release layer absorbs the gastric fluid and forms an impermeable colloid gel barrier on its surface. It produces a bulk density which is less than that of the gastric fluid and remains buoyant in the stomach until all the drug loading dose is released (U.S. Patent #4,140,755).

The biomedical application of the intragastric floating tablet technology is exemplified by the development of Valrelease by Roche for 24-hr. continuous oral administration of Valium. The development and evaluation of this hydrodynamically-balanced system will be discussed in detail by Dr. Goldberg in his lecture.

2. Intragastric Floating Drug Delivery Device

Drug delivery device can also be made to float in the stomach by the incorporation of a floatation chamber, which may be made vacuum or filled with air or a harmless gas. (Fig. 18).

A drug reservoir is encapsulated inside a microporous compartment with apertures along its bottom and top walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any contact of the stomach with the undissolved drug.

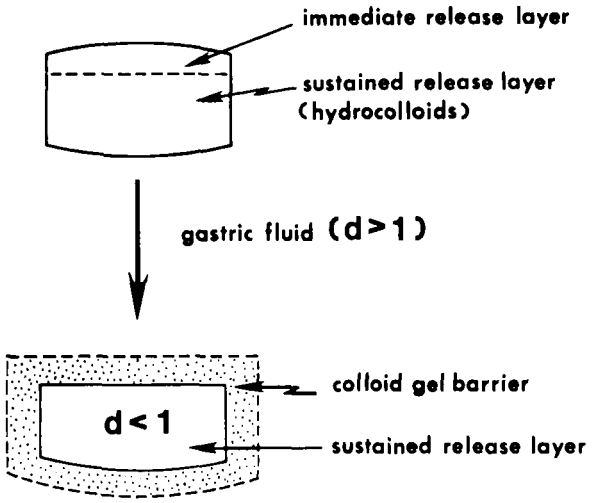


Fig. 17: Intragastric Floating Bilayer Tablet (US patent #4,140,755)

In the stomach, the floatation chamber causes the drug delivery system to float in the gastric fluids. Fluids enter through the apertures, dissolve the drugs and carry the drug solutes out of the drug delivery system for continuous transport to the intestine (U.S. Patent #4,055,178).

3. Gastro-inflatable drug delivery device

The residence time of the drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber which contains a liquid, e.g., ether, that gasifies at body temperature to cause the chamber to inflate in the stomach (Fig. 19).

The drug delivery device is fabricated by loading the inflatable chamber with a drug reservoir, which could be a drug-impregnated polymeric matrix and then encapsulating the unit in a gelatin capsule. After

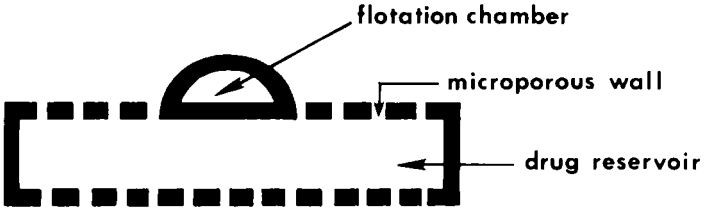


Fig. 18: Intragastric Floating Drug Delivery Device (US patent #4,055,178)

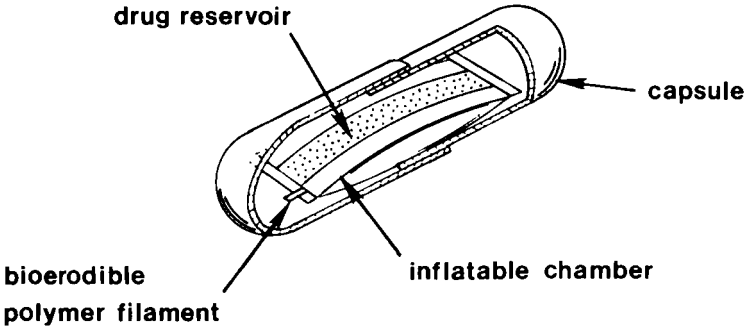


Fig. 19: Gastro-inflatable Drug Delivery Device (US patent #3,901,232)

taking orally, the capsule dissolves to release the drug reservoir and inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir in the stomach. The drug solutes continuously diffuse from the reservoir into the gastric fluids.

The inflatable chamber also contains a bioerodible polymer filament, e.g., copolymer of polyvinyl alcohol-polyethylene, which dissolves gradually in the gastric fluid to cause the inflatable chamber to collapse after a predetermined time period to permit spontaneous ejection of the system out of the stomach (U.S. Patent #3,901,232).

4. Intragastric Osmotic-controlled drug delivery system

The osmotic pressure-controlled drug release mechanism discussed earlier can also be incorporated into the gastro-inflatable drug delivery system to control the release of drug in the stomach region (Fig. 20).

It comprises an osmotic pressure-controlled drug delivery device and an inflatable floating support in a bioerodible capsule, which quickly disintegrates when it reaches the site of drug administration, like the stomach, to release the drug delivery device and inflatable floating support.

The inflatable floating support is made from a deformable hollow polymeric bag, which contains a liquid that gasifies at body temperature to inflate the bag.

The osmotic pressure-controlled drug delivery device consists of two compartments: (i) drug reservoir compartment, and (ii) osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapor and liquid, and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, gastric fluid is continuously imbibed through the semipermeable membrane into the osmotically active compartment to dissolve the osmotic active salt and to create an osmotic pressure on the collapsible bag, which, in turn, collapses to force the drug

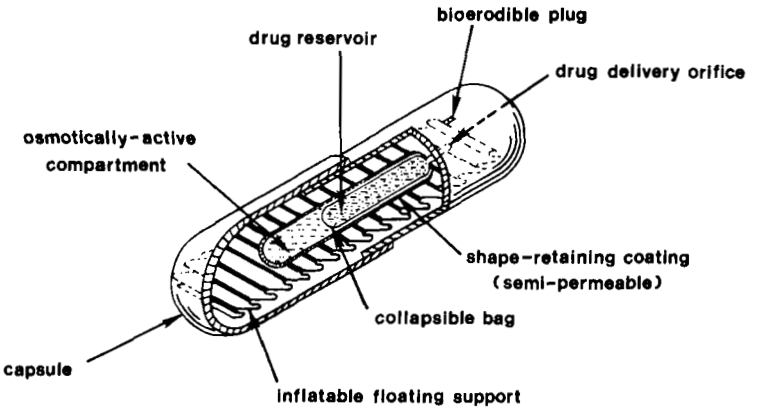


Fig. 20: Intragastric Osmotic-controlled Drug Delivery System (US patent #3,786,813)

reservoir compartment to reduce its volume and to release the drug solution through the delivery orifice (U.S. Patent 3,786,813).

The floating support also contains a bioerodible plug which erodes after a pre-determined time period to deflate the support for leaving the stomach.

5. Intra-rumen controlled release drug delivery device

It is prepared by compressing a layer of medicated polymer matrix in-between two layers of water-insoluble polymer film to form a sandwich-type composition, which is then rolled into a configuration by a gelatin band for easy oral administration. In the rumen, the band is dissolved to regenerate the original configuration for long-lasting retention in the rumen (Fig. 21).

The medicated polymer matrix is prepared by heating a homogenous mixture of a water-soluble drug and a

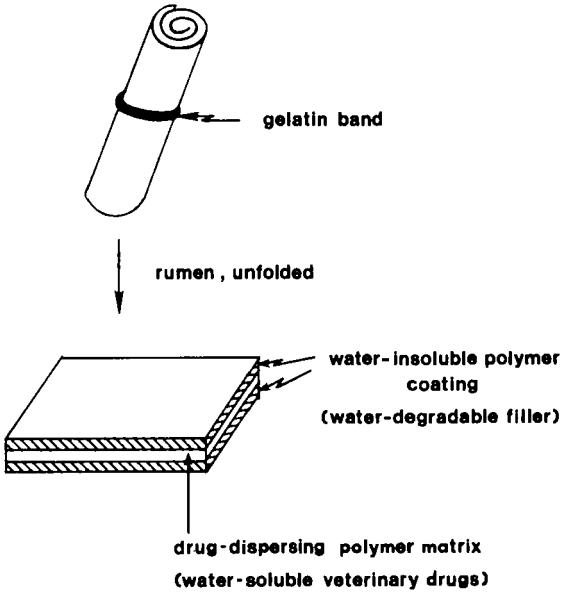


Fig. 21: Intra-rumen Controlled Release Drug Delivery Device (BE patent #867,692)

water-insoluble polymer, e.g., ethylene/vinyl acetate copolymer to 100°C and then compressing the mixture into sheets.

The polymer film is prepared by heating a homogeneous mixture of a water-insoluble ethylene/vinyl acetate copolymer and a water-degradable filler, e.g., lactose, to 100°C and then compressing the mixture to form coating films which control the rate of drug release according to the loading levels of the water-degradable filler (BE Patent #867,692).

6. Bioadhesive research

Another potential approach to extend the gastrointestinal transit time is "Bioadhesive Research" developed by Professor Robinson and his co-workers at

Bioadhesive Research

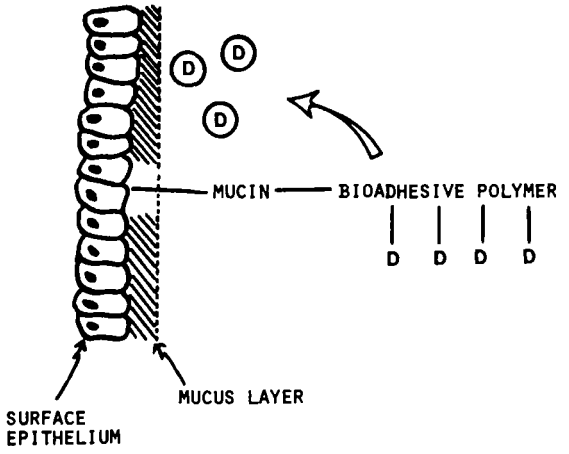


Fig. 22: Bioadhesive Research. Drug-Polymer Complex Adheres to the Mucin and Retains on the Surface Epithelium to Extend GI Transit Time (Robinson et al., University of Wisconsin)

the University of Wisconsin. It was conceptualized on the basis of the GI self-defensive mechanism.

It is known that the surface epithelium of the stomach and intestine retains its integrity during lifetime, even though it is constantly exposed to high concentrations of hydrochloric acid (as high as 0.16N) and powerful protein-splitting enzymes, like pepsin.

This self-defensive mechanism is due to the fact that the stomach, duodenum and transverse colon can produce continuously a large amount of mucus which remains closely applied to the surface epithelium. The mucus contains a glycoprotein, called mucin, which is capable of neutralizing the hydrochloric acid, withstanding the action of pepsin and thus protects the epithelial cell membrane.

The surface epithelium adherance capacity of mucin was recognized by Professor Robinson and applied to the development of bioadhesive.

The conceptualization of bioadhesive research can be shown by the illustration in Figure 22. The drug-containing bioadhesive polymer binds to the mucin molecules in the mucus layer and therefore retains on the surface eipthelium to extend GI transit time of the drug. The drug molecules are constantly released from the bioadhesive polymer for absorption.

Using the in vitro studies outlined in Fig. 23, Dr. Robinson's group were able to identify several potential bioadhesive polymers and the properties required.

By monitoring the stomach emptying time in fasted dogs, it was found that the bioadhesive polymers stay in the stomach for a duration which is 4 to 8 times longer than the non-bioadhesive polymers (Fig. 24).

Overcoming of Hepatic First-pass Elimination

If a drug is subjected to extensive hepatic "first-pass" elimination, the oral administration of the drug by controlled - or sustained-release process will produce no advantages over a conventional immediate-release drug administration. In fact, as pointed out by Dr. Welling, by controlled or sustained drug administration, drug molecules may be subjected to a greater extent of hepatic "first-pass" elimination.

In Vitro Studies

Approach:

- Use epitheial cells, grown in culture, with or without mucin.
- Add a fluorescent probe that localizes in the lipid bi-layer or protein of the cell membrane to detect the degree of binding of bioadhesive polymer.

Results:

- Cationic and anionic polymers bind more effectively than neutral polymers.
- Anionic polymers with sulphate group bind more effectively than with carboxylic group.
- Degree of binding is proportional to the charge density on the polymer.
- Highly binding polymers: Carboxymethyl cellulose, gelatin, hyaluronic acid, carbapol, polycarbophil.

Figure 23

In Vivo Studies

Approach:

To monitor the stomach emptying of the polymers in fasted dogs.

Results:

The stomach residence time:

- Bioadhesive polymers	> 6-8 hrs
- Non-bioadhesive polymers	1-1.5 hrs

Figure 24

A typical example is the metabolism of acetaminophen by the microsomal enzymes in the liver into glucuronide and sulfate for elimination through the urinary excretion (Fig. 25). This hepatic "first-pass" metabolism accounts for 90-100% of the elimination of acetaminophen dose. That means that less than 10% of the oral dose of acetaminophen remains intact and pharmacologically active. (5)

1. Physical approaches

However, the hepatic metabolism of acetaminophen can be used productively to protect the metabolism of opiate-type narcotic drugs by the UDP-glucuronyl transferase in the intestinal and hepatic microsomes using the mechanism of competitive metabolism (Fig. 26). Due to the preferential metabolism of acetaminophen, the metabolic elimination of narcotic drugs is significantly reduced, thereby greatly enhancing the oral bioavailability and pharmacogic activity of the narcotic drugs.

2. Chemical approaches

The metabolic elimination of narcotic drugs can also be minimized by the formation of aspirin derivative (Fig. 27). After hepatic "first-pass" metabolism, the pro-drug, narcotic-aspirinate, is converted back to narcotic drugs and aspirin to achieve a synergic analgesic activity.

3. Buccal and Sublingual Drug Administration

It has been known for centuries that after buccal and sublingual administrations, drug solutes are rapidly absorbed and transported through facial veins, internal

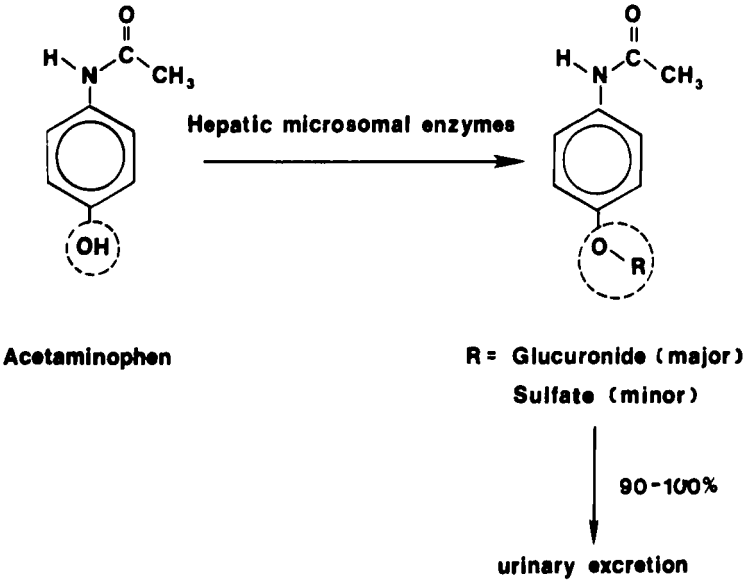


Fig. 25: Hepatic "First-Pass" Metabolism
(Gilman et al, 1980)

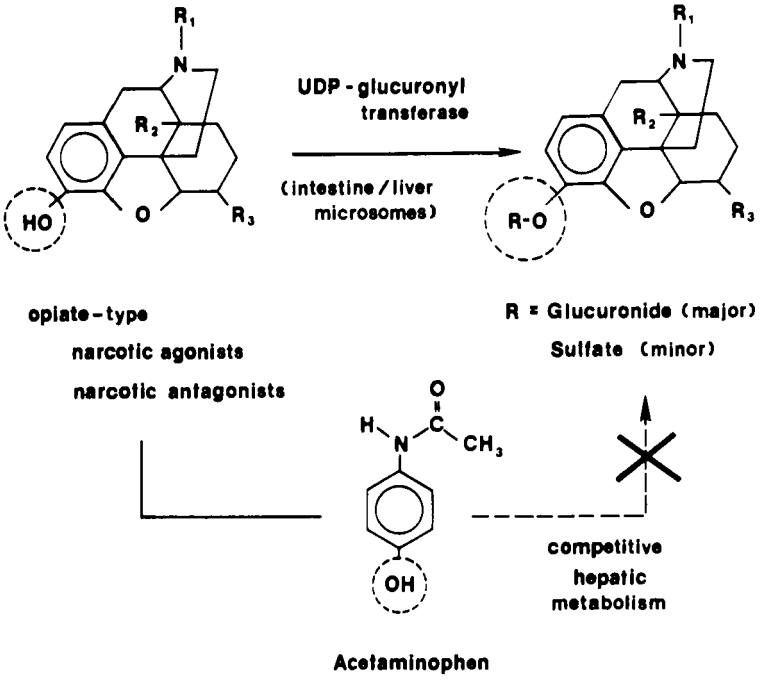


Fig. 26: Competitive Hepatic Metabolism
(Weinstein et al, 1973: Del Villar et al, 1974)

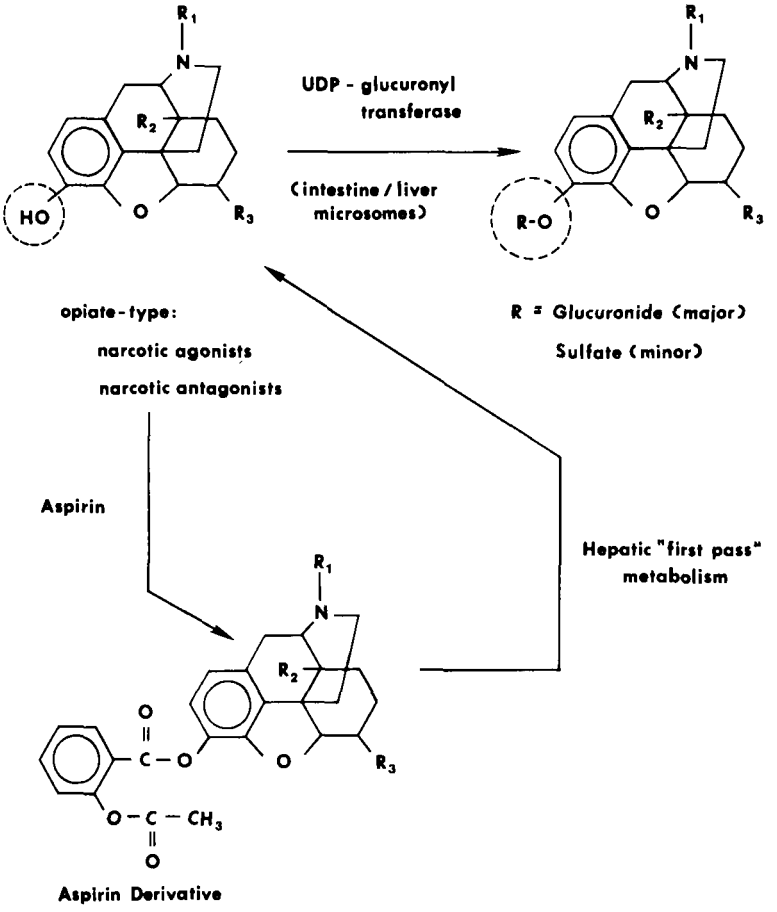


Fig. 27: Hepatic Biotransformation

jugular vein and braciocephalic vein, and then drained into systemic circulation. Therefore, the buccal and sublingual drug administrations can be used to bypass the hepatic "first-pass" elimination.

It is also recognized that the buccal and sublingual drug absorptions are mostly rapid in action and short acting in duration. For example, by sublingual administration, nitroglycerin is rapidly absorbed and its peak plasma level is reached within 1-2 min. But the blood

level declines rapidly to the level below the therapeutic concentration within 10-15 min. Two methods have been developed to prolong the duration of buccal and sublingual drug administrations:

1) Transmucousal sustained-release troches

The sustained-release troches is developed for long-term administration (1-8 hrs.) of locally - or systemically active drugs through buccal or sublingual mucosa (Fig. 28).

It is prepared by blending drug with saliva-activated polymeric adhesive and then compressing the mixture to form troches.

In the oral cavity, the polymeric adhesive in the troche is activated by the saliva and become adhesive, which renders the troche adhered to the oral mucosa in the buccal or sublingual areas. The drug solutes are continuously released for transmucosal absorption into the systemic circulation.

Several compositions have been developed as the saliva-activated polymeric adhesive:

a) Hydroxypropyl Cellulose ($\geq$80%)
Ethyl cellulose ($\leq$20%)

Hydroxypropyl cellulose and ethyl cellulose are mixed together at dry state and humidified to increase the moisture content to $\geq$85% and then dehumidified to a moisture content of less than 10% to form the

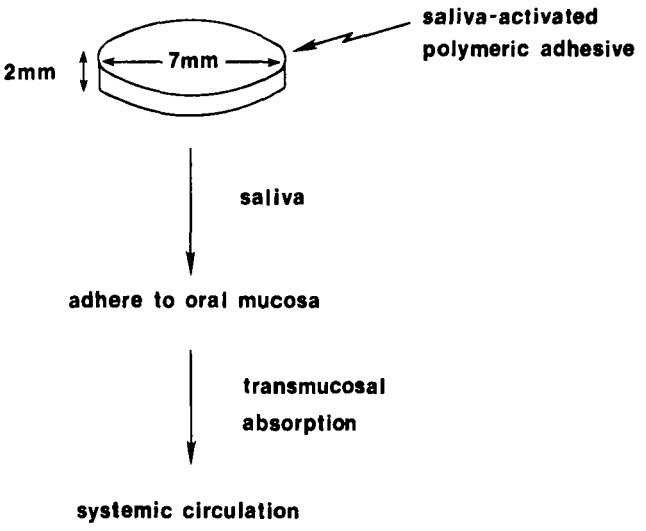


Fig. 28: Transmucousal Sustained-release Troches

saliva-activated polymeric adhesive (GB Patent #1,279,214; ZA Patent #7,805,528). It is exemplified by the development of Susadrin transmucosal tablet by Forest Lab for Merrell Dow. It will be discussed in more detail by Dr. Schor in his lecture.

b) Hydroxypropyl cellulose (0.02 - 2%)
Polyacrylic acid/Na salt (0.2%)

The saliva-activated polymeric adhesive can also be prepared from the combination of hydroxypropyl cellulose and polyacrylic acid (or sodium salt) mixed at a fixed ratio of 1 to 0.1 - 10, and compressing the mixture, drug and magnesium stearate (0.5%) into disc with hardness of 20 Kg (J Patent #5-4,041,320).

c) Sodium polyacrylate (10-60%)

Sodium polyacrylate, by itself, can also be formulated as the saliva-activated polymeric adhesive (J Patent #7-9,038,168).

d) Alkyl acrylate (<30%)
Acrylamide/vinyl pyrrolidone (>70%)

Alkyl acrylate and homopolymer or copolymer of acrylamide/vinyl pyrrolidone can be formulated as the saliva-activated polymeric adhesive by solvent casting technique (GB Patent #2,021,610).

2. Oral sustained-release microcapsules

It is also designed for sustained release of drugs in the oral cavity, from 1 to 8 hrs., without interfering with chewing, speech, sleeping or breathing (Fig. 29).

It is prepared by microencapsulating the drug with different thicknesses of polymer coating made from hydroxypropyl cellulose or other polymeric materials and coating the microcapsules with oral adhesive, e.g., pectin, and then compressing the coated microcapsules into a tablet suitable for oral cavity placement (U.S. Patent #3,911,099).

2. Rectal Drug Administration

The rectal route of drug administration has been frequently used in several European countries, whereas it is not very popular in the United States (Fig. 30).

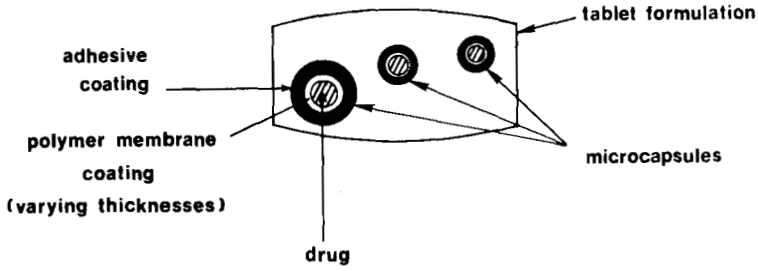


Fig. 29: Oral Sustained-release Microcapsules
(US patent #3,911,099)

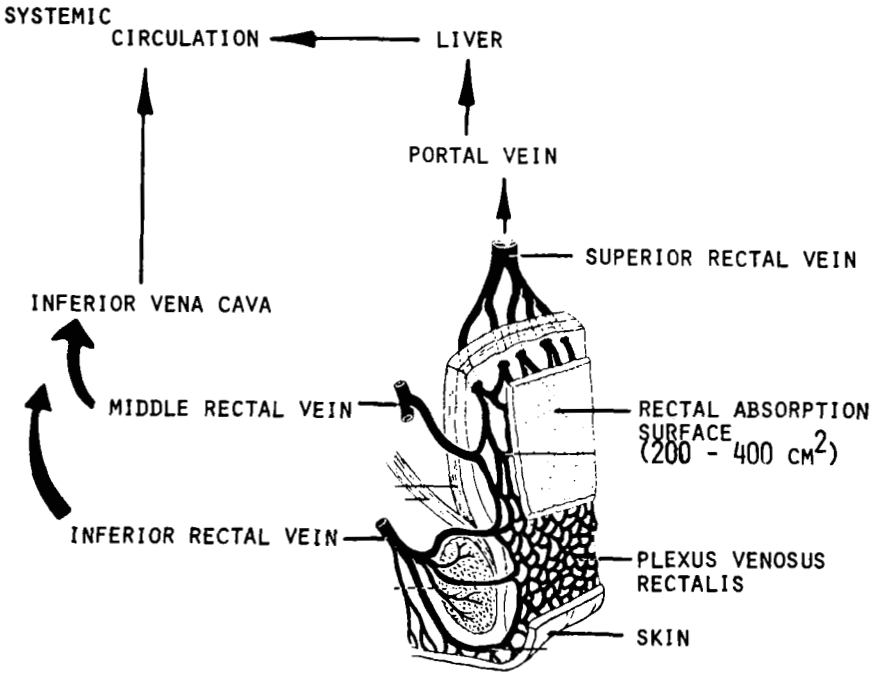


Fig. 30: Human Rectum : Venous Drainage Network
(Tondury, 1959)

It was reported that when drug is delivered to the lower region of the rectum, it is absorbed into the inferior and middle rectal veins, then passes into the inferior vena cava, and finally drains into the systemic circulation, thereby bypassing the portal vein and the hepatic "first-pass" metabolism. (6)

On the other hand, if the drug is delivered to the upper region of the rectum, it will probably be absorbed and then transported via the superior rectal veins into the portal vein and subjected to hepatic "first-pass" elimination before entering the systemic circulation. However, this anatomical situation is complicated by anastomoses among the rectal veins underneath the rectal mucosa (absorption sruface).

The effect of rectal administration on the hepatic "first-pass" metabolism of drugs can be demonstrated by the systemic bioavailability of a high-clearance drug, e.g., Lidocaine.

Studies conducted in 6 healthy volunteers indicated that rectal absorption of lidocaine in aqueous solution results in a systemic bioavailability as high as 69% (Fig. 31). On the other hand, the oral administration of lidocaine only achieves a system bioavailability of 30.5%. It is estimated that rectal administration of lidocaine has resulted in 55% of the dose bypassing the hepatic "first-pass" metabolism. (6,7)

Effect of the sites of rectal infusion on the systemic bioavailability of lidocaine was also investigated (Fig. 32). Results suggested that the infusion site located at only 2 cm from the anus produces a greater system bioavailability of lidocaine than the infusion site located at 4 cm away[8]. It implies that

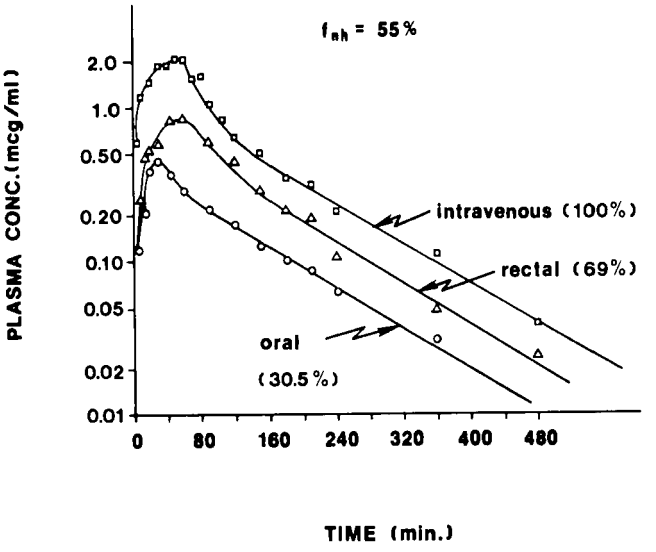


Fig. 31: Comparative Systemic Bioavailability of Lidocaine in Human (De Boer & Breimer, 1980: De Boer et al, 1979)

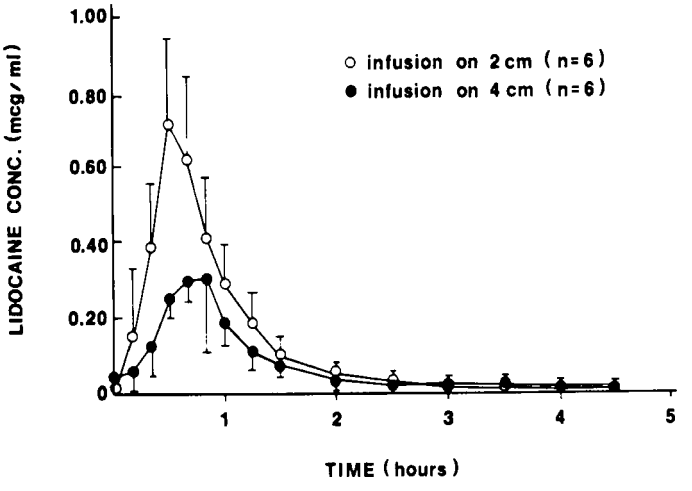


Fig. 32: Effect of Rectal Infusion Sites on Systemic Bioavailability of Lidocaine in Rats (De Boer et al, 1982)

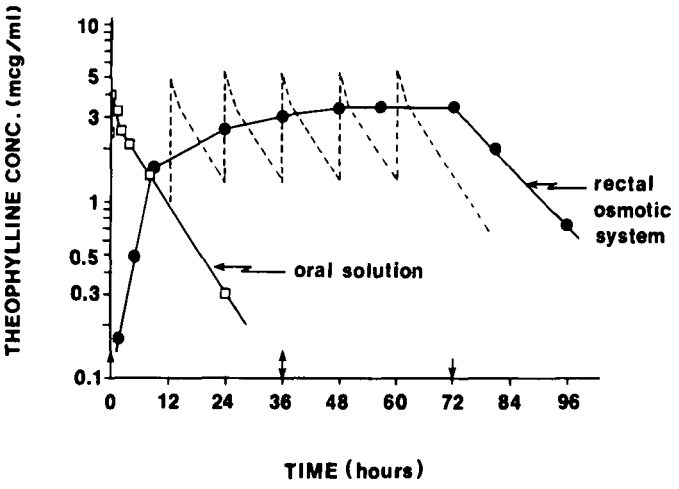


Fig. 33: Comparative Plasma Profile of Theophylline in Humans (De Leede et al, 1981)

the rectal absorption via inferior rectal veins has a greater chance to bypass the hepatic "first-pass" metabolism.

Using a specially designed rectal osmotic system (9), the blood level of theophylline was significantly prolonged by applying one unit every 36 hours (Fig. 33). A fairly constant blood level was also maintained. On the other hand, oral administration of theophylline in solution every 12 hours, a fluctuated blood level of theophylline was observed (10).

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