Pharmaceutical Polymers
Drug Delivery and Pharmaceutics
**Drug Delivery Systems Terminology**

**Drug delivery systems**
Conventional formulations, e.g., tablet, capsule, ointment, and solutions, that release most or all loaded drug(s) immediately without any control. Thus, conventional formulations are usually called “immediate release” or IR formulations.

**Controlled release drug delivery systems**
Newer formulations that have a built-in technology to control the drug release kinetics over time. The term “controlled” had an additional meaning of maintaining relatively constant drug concentration in the blood over time. However, maintaining a constant drug concentration is difficult, especially for oral controlled release formulations. The formulations are effective as long as the drug concentrations are maintained within the therapeutic index, i.e., above the minimum effective drug concentration and below the maximum safe concentration.

Controlled release drug delivery systems have also been called
- Sustained-release Systems
- Extended-release Systems
- Delayed-release Systems
- Therapeutic Systems

**Drug Delivery Systems = Drug + Everything Else (Excipients)**

Excipients should be “generally regarded as safe (GRAS)” materials
The book can be downloaded from the folder “6. Pharmaceutical Polymers”
Norplant: Made of Silicone rubber
36 mg levonogestrel.
85 μg/day (later 30 μg/day) up to 7 years.
Therapeutic Index (TI) = $\frac{C_{\text{max}}}{C_{\text{min}}}$

**TI values of selected drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>TI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>$\infty$</td>
</tr>
<tr>
<td>Triphenylamine</td>
<td>19,000</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>2,300</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>1,400</td>
</tr>
<tr>
<td>Penicillin</td>
<td>$&gt;100$</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>20-40</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>2-7</td>
</tr>
<tr>
<td>Quinidine</td>
<td>2-3</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Candidate drugs for sustained release?

Zero-order release system?
Rationale of Controlled Drug Delivery Systems

Which of the following PK profiles is the best?

Theoretical answer vs. Practical answer

Consider how a new drug is tested and approved.
Consider what does personalized medicine mean.
Pre-1950
The 1906 Pure Food and Drugs Act

The Pure Food and Drug Act (1906)

Signed by President Theodore Roosevelt in 1906.

It was commonly known as the Harvey Law. But it had many shortcomings and became mute in 1930.

Commemorative 50th Anniversary of Pure Food and Drug Laws stamp first issued by the U.S. Postal Service on June 27, 1956

The Federal Food, Drug, and Cosmetic Act (1938)

Signed by President Roosevelt in June 1938.

New drugs have to be tested for safety before marketing, and the result has to be submitted to FDA in a new drug application (NDA).

Point: Drink a milk from a grocery → Safe


The Kefauver-Harris Amendments (1962)

Drug manufacturers must prove that their products were both safe and effective for approval.

Safety and effectiveness should consist of “adequate and well-controlled” scientific experiments carried out by “experts qualified by scientific training.”

Thalidomide devastation

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856.htm
The Food and Drug Administration (FDA)
Medicine Shouldn't Be A Luxury

A patent medicine in 1800s.

TikTok @_chelittaditt

Forbes Jan. 2020
'The Poison Squad' tells the story of government chemist Dr. Harvey Wiley who, determined to banish these dangerous substances from dinner tables, took on the powerful food manufacturers and their allies. (Season 32, Episode 2).
"By the end of nineteenth century, food was dangerous. Lethal, even. “Milk” might contain formaldehyde, most often used to embalm corpses. Decaying meat was preserved with both salicylic acid, a pharmaceutical chemical, and borax, a compound first identified as a cleaning product.

This was not by accident; food manufacturers had rushed to embrace the rise of industrial chemistry, and were knowingly selling harmful products. Unchecked by government regulation, basic safety, or even labelling requirements, they put profit before the health of their customers. By some estimates, in New York City alone, thousands of children were killed by “embalmed milk” every year. Citizens–activists, journalists, scientists, and women’s groups–began agitating for change. But even as protective measures were enacted in Europe, American corporations blocked even modest regulations. Then, in 1883, Dr. Harvey Washington Wiley, a chemistry professor from Purdue University, was named chief chemist of the agriculture department, and the agency began methodically investigating food and drink fraud, even conducting shocking human tests on groups of young men who came to be known as, "The Poison Squad."

https://www.penguinrandomhouse.com/books/312067/the-poison-squad-by-deborah-blum/9781594205149/
The Jungle (1906)
Sinclair. "I aimed at the public's heart (workers' right), and by accident I hit it in the stomach."

Upton Sinclair's The Jungle
- Laws passed after Congress' investigation:
  - **Meat Inspection Act**
    - USDA (US Department of Agriculture)
  - **Pure Food and Drug Act**
    - FDA (Food and Drug Administration)

Criticism of Upton Sinclair's The Jungle
- Was Sinclair too biased? Was Sinclair just anti-capitalist trying to attack the meat industry? Did Sinclair exaggerate about what was really taking place in the meat-packing factories?
- The Jungle's fictitious characters tell of men falling into tanks in meat-packing plants and being ground up with animal parts, then made into 'Durham's Pure Leaf Lard.'
- Historian Stewart H. Holbrook argues this was nonsense. Sinclair's The Jungle was far from reality:
  - "The grunts, the groans, the agonized squeals of animals being butchered, the rivers of blood, the...steaming masses of intestines, the various stenches...were displayed along with the corruption of government inspectors and, of course, the callous greed of the ruthless packers."

https://www.slideshare.net/iRawrPanda/upton-sinclair-and-critics-of-the-jungle
Frances Kelsey: Medical officer at FDA Refusal to allow NDA of thalidomide based on insufficient safety data.

Thalidomide’s horrifying effects on newborns became known in 1962.
Distribution of two million tablets by Merrell for investigational use.
History Repeats Itself

Different subjects but the same cycle:
Ignorance, Outrage, & New law protecting consumers

Industries for profit

Food industry
Livestock (water consumption and methane (CH₄) emission)
Fishery & Fishing industry
Tobacco industry
Opioid pain killers
Plastics industry
Importance of the Food & Drug Administration
From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of $2.6 billion, including the cost of the many potential medicines that do not make it through to FDA approval. Less than 12% of the candidate medicines that make it into Phase 1 clinical trials will be approved by the FDA.

Drug Potency

IND: Investigational new drug application
NDA: New drug application
BLA: Biologics license application

IND: Investigational new drug application
NDA: New drug application
BLA: Biologics license application
FDA Drug Approval Process

What is a drug as defined by the FDA? A drug is any product that is intended for use in the diagnosis, cure mitigation, treatment, or prevention of disease; and that is intended to affect the structure or any function of the body.

PRE-CLINICAL: Drug Sponsor’s Discovery and Screening Phase

1. **Drug Developed**
   Drug sponsor develops a new drug compound and seeks to have it approved by FDA for sale in the United States.

2. **Animals Tested**
   Sponsor must test new drug on animals for toxicity. Multiple species are used to gather basic information on the safety and efficacy of the compound being investigated/researched.

3. **IND Application**
   The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from initial testing that include the drug’s composition and manufacturing, and develops a plan for testing the drug on humans.

CLINICAL: Drug Sponsor’s Clinical Studies/Trials

3. **Phase 1: 20-80**
   The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal here is to determine what the drug’s most frequent side effects are and often, how the drug is metabolized and excreted.

4. **Phase 2: 100s**
   The typical number of patients used in Phase 2; this phase emphasizes effectiveness. The goal here is to obtain preliminary data on whether the drug works in people who have certain disease condition. Short-term side effects are studied.

   At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.

5. **Phase 3: 1000s**
   The typical number of healthy volunteers used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and uses the drug in combination with other drugs.

http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm295473.htm
Who reviews new drug submissions? A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists review the drug sponsor’s data and proposed labeling of drugs.

NDA REVIEW: FDA’s New Drug Application (NDA) Review

- **6 Review Meeting**
  FDA meets with a drug sponsor prior to submission of a New Drug Application.

- **7 NDA Application**
  The drug sponsor formally asks FDA to approve a drug for marketing in the U.S. by submitting an NDA. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

- **8-9 Application Reviewed**
  After an NDA is received, FDA has 60 days to decide whether to file it so it can be reviewed. If FDA files the NDA, the FDA review team is assigned to evaluate the sponsor’s research on the drug’s safety and effectiveness.

- **10 Drug Labeling**
  FDA reviews the drug’s professional labeling and assures appropriate information is communicated to health care professionals and consumers.

FASTER APPROVALS

The Accelerated Approval program. The Fast Track program.

**Example**

FDA Fast-Tracks Experimental Ebola Drug Zmapp

Promising Ebola Drug ZMapp: The Real Lessons of an Inconclusive Study
(http://www.livescience.com/56468-ebola-drug-zmapp-study-inconclusive.html)

COVID-19 Vaccine Development

POST-MARKETING: FDA’s Post-Approval Risk Assessment Systems

**Phase 4**

Because it’s not possible to predict all of a drug’s effects during clinical trials, monitoring safety issues after drugs get on the market is critical. The role of FDA’s post-marketing safety system is to detect serious unexpected adverse events and take definitive action when needed.

http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm295473.htm
FDA's Center for Drug Evaluation and Research (CDER) evaluates new drugs before they can be sold. The center’s evaluation not only prevents quackery, but also provides doctors and patients the information they need to use medicines wisely. CDER ensures that drugs, both brand-name and generic, are effective and their health benefits outweigh their known risks.

BLA: Biologics license application
NME: New molecular entity
Why is it So Difficult to Develop a New Drug?

Drugs don’t differentiate:
Not enough sound therapeutic hypotheses!

No rationale in picking targets based on human biology

No human phenotype for drug efficacy testing

Incomplete understanding of biological function or molecular mechanism of disease-associated variants, genes & pathways

Conventional modalities (e.g., small molecules, monoclonal antibodies) modulate <20% of targets

New modalities are desperately needed, but today are limited by delivery and pharmacological properties

Precision medicine: patient subsets for whom therapeutic intervention works better

http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Research/DrugForum/2017%20MAR%208/Plenge%20-%20Session%20IV.pdf
Flattening the slope

A glimmer of hope in the fight against a dreadful illness

ALZHEIMER’S disease is incurable, and only barely treatable. Drugs such as Aricept bring temporary relief, but nothing halts its onward march. There was therefore a lot of excitement, among researchers and journalists alike, in the lead-up to a lecture given on July 22nd at the Alzheimer’s Association International Conference, in Washington, DC. The talk was entitled “Delayed Start Studies in the Assessment of Potential Disease Modifying Effect”. Translated into English, that meant the researchers presenting the paper, who work for Eli Lilly, a big pharmaceutical company, thought they had come up with something which slows down the illness’s progression.

Their something is an antibody, called solanezumab by its inventors, that sticks to beta amyloid. This is one of the proteins which contribute to the plaques and tangles of matter in the brain that are characteristic of the disease. The researchers hoped, when they began the study, that solanezumab might slow down plaque formation and give a patient extra years of lucidity.

When Lilly tested the drug in 2013, they found little evidence of success—except in those with mild, early-onset Alzheimer’s, for whom there were hints that the progression of the disease had been slowed. But by extracting this group from the rest, and concentrating on them, the firm’s scientists have discovered something more hopeful.

Their delayed-start trial worked like this. Three and a half years ago, the 1,300 qualifying patients were divided into two groups. One lot were put on solanezumab immediately. The others were given a placebo for the trial’s first 18 months, and thereafter switched to the real thing, which they have now been taking for two years.

In cognitive tests that use a quantitative scale of dementia’s effects, those in the delayed group fell behind the others in the months when they were on the placebo. Once they switched to the drug, their rate of decline slowed to match that of those who had been on treatment since the beginning. The antibody appeared, in other words, to be slowing the disease’s progress. This is nowhere near a cure. It may, however, point the way to one. Perhaps a different antibody, or a combination, would have a greater effect.

Solanezumab is a humanized monoclonal IgG1 antibody directed against the mid-domain of the Aβ peptide. It recognizes soluble monomeric, not fibrillar, Aβ. The therapeutic rationale is that it may exert benefit by sequestering Aβ, shifting equilibria between different species of Aβ, and removing small soluble species of Aβ that are directly toxic to synaptic function. In preclinical research, a single injection of m266, the mouse version of solanezumab, reversed memory deficits in APP-transgenic mouse models while leaving amyloid plaques in place, raising the prospect of targeting the soluble pool of Aβ.

Lilly Announces Top-Line Results of Solanezumab Phase 3 Clinical Trial

INDIANAPOLIS, Nov. 23, 2016 /CNW/ -- Eli Lilly and Company (NYSE: LLY) today announced that solanezumab did not meet the primary endpoint in the EXPEDITION3 clinical trial, a phase 3 study of solanezumab in people with mild dementia due to Alzheimer's disease (AD).

Patients treated with solanezumab did not experience a statistically significant slowing in cognitive decline compared to patients treated with placebo (p=.095), as measured by the ADAS-Cog14 (Alzheimer's Disease Assessment Scale-Cognitive subscale). https://investor.lilly.com/releasedetail.cfm?ReleaseID=1000871

Failed Alzheimer’s trial does not kill leading theory of disease

The drug, and others based on the ‘amyloid hypothesis’, are still being tested in other, different trials.

Alison Abbott & Elie Dolgin.
Nature 540: 15-16, 2016

Merck has decided to abandon efforts to market a closely watched experimental cholesterol medicine after mediocre test results. Merck's decision Wednesday to not seek regulatory approval after years of testing marks the fourth time this type of once-promising drug has been scrapped. Merck had continued to study its drug, a so-called CETP inhibitor called anacetrapib, long after rivals had given up on similar drugs.

Merck raised hopes when it announced in June that anacetrapib not only lowered cholesterol, but also reduced heart attacks, deaths and other heart disease complications. But in August it disclosed the pill only cut those risks 9 percent. That would have limited sales of the drug, if it had won regulatory approval, in part because cheap, genetic statin drugs lower cholesterol well for most people.

Generic versions of brand-name statin cholesterol pills including Lipitor, Crestor and Merck's own Zocor now cost $10 to $20 a month. Repatha and Praluent, two new injected medicines in a different drug category that have been shown to dramatically reduce cholesterol, cost $14,000 a year.

Georgetown University cardiologist Dr. Allen J. Taylor said he thinks the drug would be approved by the Food and Drug Administration despite its "relatively weak benefit."
"If you were discussing this with patients," Taylor said, "you would have to tell them that when you start this, you'll have to take it for four years to have a 1 percent chance of preventing an event," meaning a heart attack or a procedure such as bypass surgery or implanting a stent to keep an artery open.

Linda A. Johnson. 10/12/2017
Hidden Side Effects: Medical Studies Often Leave Out Adverse Outcomes. A new analysis estimates that for nearly half of clinical studies, data goes “missing” when published.

Starting this month, U.S. investigators conducting clinical trials will have to make all their findings publicly available—no matter what outcome a study has—thanks to a new rule from the U.S. Department of Health and Human Services and the U.S. National Institutes of Health. Meanwhile the Evidence-Based Medicine Data Lab at the University of Oxford released a new online tool called TrialsTracker that reveals exactly who is withholding data.
Slower Progress in New Drug Development

1964
- Liposome (Bangosome)
- UNIVAC 1108 (1 MB memory)

1994
- Taxol® Paclitaxel in PEGylated Castor Oil
- Abraxane® Paclitaxel in Albumin Complex

2005
- Movantik RNAi in PEGylated Lipid Nanoparticle

2018
- Onpattro® RNAi in PEGylated Lipid Nanoparticle

2021
- Laptop (32 GB memory)
- Comirnaty® PEGylated CAR-T Lipid Nanoparticle

1990
- Adagen® PEGylated Protein

2014
- Movantik (naloxol) tablets

2017
- Kymriah® CAR-T Gene Therapy

2021
- Comirnaty® PEGylated Lipid Nanoparticle

Timeline:
- 1942: ENIAC
- 1946: 1st Elec. Mech. computer
- 1959-1963: IC
- 1964-1979: Macintosh
- 1984: Mark 1, 1st Elec. Mech. computer
- 2021: Laptop (32 GB memory)
Controlled Drug Delivery Mechanisms
Evolution of Controlled Drug Delivery Systems

**Controlled Drug Delivery**

- **From 12 hours to 5 years**
  - 1952: Spansule® Dissolution-control
  - 1964: Liposome
  - 1970: Ocusert® Diffusion-control
  - 1974: Transderm Scop® Osmosis
  - 1975: OROS® dissolution control
  - 1974: InFed® Iron-Dextran Complex
  - 1990: Norplant® Implant
  - 1998: Lupron® Depot

**Nanomedicine**

- 1952: Iron-Dextran Complex
- 1974: Liposome
- 1974: Paclitaxel in PEGylated Castor Oil
- 1990: Adagen® PEGylated Protein
- 2000: Rapamune® Nanocrystal
- 2005: Abraxane® Paclitaxel-Albumin Complex

**Precision Medicine & Health Equity**

- 2005: Comirnaty® PEGylated Lipid NP
- 2019: Rebelsus® Oral Peptide Tablet
- 2018: Onpattro® PEGylated siRNA in PEGylated Lipid Nanoparticle
- 2017: Kymriah® CAR-T Gene Therapy
- 2014: Movantik® PEGylated naloxol

**Overcoming Biological Barriers**

- 2017: Movantik® Peptide, Protein, & RNA Drugs

**Long-Term Treatment for Chronic Diseases**

- 2014: Movantik® PEGylated naloxol

**Targeted Delivery**

- 1990: Ab-Drug Conjugate Mylotarg™
- 2000: InFed® PEGylated Liposome
- 2000: Taxol® Paclitaxel in PEGylated Lipid
- 2005: Abraxane® Paclitaxel-Albumin Complex

**Precision Medicine** & **Health Equity**

- 2014: Movantik® PEGylated naloxol

**Controlled Drug Delivery**

- 1950: 12 hours
- 1960: 5 years
- 1970: Controlled Drug Delivery
- 1980: Nanomedicine
- 1990: Precision Medicine & Health Equity
- 2000: Evolution of Controlled Drug Delivery Systems
- 2010: Overcoming Biological Barriers
- 2020: Long-Term Treatment for Chronic Diseases
- 2030: Targeted Delivery
- 2040: Precision Medicine
- 2050: Health Equity
**Diffusion**

Movement of molecules from high concentration to low concentration in water (or in solvent). Both solute and solvent move.

**Osmosis**

Movement of solvent (water) across a semipermeable membrane from high to low solvent concentration. Only solvent move.

\[ D = \frac{kT}{6\pi\eta r} \]

\[ x = \sqrt{2Dt} \text{ cm}^2/\text{s} \]

(One dimensional diffusion)

https://sciencenotes.org/osmosis-vs-diffusion-definition-and-examples/

https://openoregon.pressbooks.pub/mhccbiology101/chapter/diffusion/
Controlled Release Dosage Forms: Major Components

Drug + Drug Delivery Module + Platform
- Reservoir
- Delivery Portal (Exit)
- Energy Source
- Rate Controller

Transdermal Patch
- Occlusive Backing
- Drug Reservoir
- Rate-controlling Membrane
- Contact Adhesive
- Protective Liner

Osmotic Tablet
- Water
- Drug
- Semi-permeable membrane
A fresh nonporous, homogeneous polymer membrane.

Concentration on the donor side $C_d$ remains constant. The concentration on the receptor side $C_r$ is zero at $t = 0$. 

Sink condition: $C_r = 0$
A nonporous, homogeneous polymer membrane presaturated with a drug

Drug Release through a Polymer Membrane (Solution-Diffusion Membrane)

- **Suspended Drug**
- **Membrane**
- **Aqueous Solution**
  - **Cd**
  - **Partition**
  - **Diffusion**

**Burst effect**

**Sink condition**

**Lag time**
Cumulative Drug Release

Slope = Steady-state release rate

Once steady state has been achieved, zero-order release is observed regardless of the membrane thickness.

\[ t_B = \frac{h^2}{3D} \]
\[ t_L = \frac{h^2}{6D} \quad (\text{Lag time}) \]

\[ M = S \cdot D \cdot K \frac{\Delta C}{h} (t + \frac{h^2}{3D}) \]
\[ M = S \cdot D \cdot K \frac{\Delta C}{h} (t - \frac{h^2}{6D}) \]
# Mechanisms of Controlled Drug Release

<table>
<thead>
<tr>
<th>Physical Mechanisms</th>
<th>Chemical Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dissolution</td>
<td>5. Chemical Degradation</td>
</tr>
<tr>
<td>Reservoir System</td>
<td>6. Enzymatic Degradation</td>
</tr>
<tr>
<td>Matrix System</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Reservoir = Encapsulated)</td>
</tr>
<tr>
<td>2. Diffusion</td>
<td></td>
</tr>
<tr>
<td>Reservoir System</td>
<td>(Monolithic = Matrix)</td>
</tr>
<tr>
<td>Monolithic System</td>
<td></td>
</tr>
<tr>
<td>Monolithic Solution System</td>
<td></td>
</tr>
<tr>
<td>Monolithic Dispersion System</td>
<td></td>
</tr>
<tr>
<td>3. Osmosis</td>
<td></td>
</tr>
<tr>
<td>4. Ion-Exchange</td>
<td></td>
</tr>
</tbody>
</table>
**Reservoir System (= Encapsulated Dissolution System)**

Drug → Water-soluble polymer membrane

Soluble after 3 h → 6 h → 9 h

Dissolution of the polymeric material (e.g., PEG) is the key to this mechanism. All of the polymers used must be water soluble or degradable.

**Matrix Dissolution System**

The drug is homogeneously distributed throughout the polymer matrix.

As the polymer matrix dissolves, drug molecules are released.
**Reservoir System (= Encapsulated Diffusion System)**

Dissolution of the polymeric material is the key to this mechanism. All of the polymers used must be water soluble or degradable.

**Monolithic Diffusion System**

The drug is homogeneously distributed throughout the polymer matrix. As the polymer matrix dissolves, drug molecules are released.

**Nonporous membrane**

**Microporous membrane**

Drug must diffuse through solution-diffusion membrane

Drug is released through micropores (usually filled with water or oil)
1-Dimension Reservoir Device (Slab)

\[ M = \frac{S \cdot D \cdot K \cdot \Delta C \cdot t}{h} \]
\[ \frac{dM}{dt} = \frac{S \cdot D \cdot K \cdot \Delta C}{h} \]

\( \Delta C = C_s - C \)

Drug release is zero order.

**Norplant® Subdermal Implant**

Six matchstick-size silicon rubber rods inserted into the upper arm. Each rod contains 36 mg levonogestrel. The system releases 85 mg/d initially, which declines to 30 mg/d during its useful life (up to 7 years).

**Microporous polypropylene film (Celgard®)**

Maintain constant flow and flame height, regardless of ambient pressure and fuel level.
Diffusion-Controlled Monolithic System

Monolithic Solution System  Monolithic Dispersion System

The maximum drug concentration is the drug solubility in solution. The maximum drug concentration depends on the solid drug content.

Decrease in release rate due to increase in diffusion path length
**Osmosis-Controlled System**

**TYPICAL DELIVERY RATE FROM OROS®**

**Mean plasma methylphenidate concentrations with Concerta and Immediate-release tablet.**

**Special delivery**

A three-layer Concerta wafer, used in the treatment of attention-deficit hyperactivity disorder, releases methylphenidate in a semi-permeable manner.

1. Drug layer 1 (less concentrated)
2. Drug layer 2 (more concentrated)
3. Push layer (water-absorbing polymer)

**Mean plasma methylphenidate concentrations with Concerta and Immediate-release tablet.**

**DUROS® implant technology DURECT**

**DUROS VS. CONVENTIONAL DRUG ADMINISTRATION**

- **CONCERTA® 18 mg od**
- **Methylphenidate 5 mg tid**

**Release rate in milligrams per hour**

**TIME: 9 AM, 2 PM, 5 PM, 8 PM, 11 PM, 2 AM**

- **1.** Osmotic agent dissolves, delivering a high initial dosage of methylphenidate.
- **2.** Low-concentration medication is released through semi-permeable membrane.
- **3.** Highly concentrated medicine slowly starts to blend with less concentrated layer.
- **4.** As the push-layer continues to expand, the drug is depleted and dosage gradually decreases.

**126(F) • FORTUNE • July 21, 2003**
Seawater undergoes reverse osmosis, in which high pressure forces the water through membranes that remove impurities.
Despite the name, the most common type of water filter does not produce chemically pure water. If it did, the water would not taste right to us. Instead, the filter's activated carbon and ion-exchange resin remove harmful ions and molecules from water, leaving those that make it pleasant to drink.

This sorption has a practical aspect it expands the life of the filter. The filter's capacity for chemicals is limited by the laws of thermodynamics. As the water becomes more pure and odorous, the filter becomes more impure and odorous. This accumulating disorder and the associated consumption of the filter's potential energy lessens its effectiveness. By having innocuous and durable chemicals, such as fluoride, in the water, the filter avoids such demise.

**ACTIVATED CARBON** is a highly porous material that acts as a sponge for the removal of molecules like benzene (C) and some pesticides (UF and others). Such molecules bind onto surfaces in the activated carbon's porous network of large and small pores. A single gram of activated carbon can contain millions of tiny, interpenetrating pores. This makes it difficult for large ions to enter and escape from the pores, thereby increasing the filter's lifespan.

**ION EXCHANGE RESIN** is a specially prepared plastic that exchanges ions in water with other ions, such as it exchanges the sodium ions for other ions. This process helps to remove mineral ions from the water, thereby softening it and making it more suitable for drinking.

**Dextromethorphan** is an ingredient in some cough remedies, and its chemical structure is shown below. It is a pharmacologically active compound used in the treatment of dry cough and some forms of pain.

---

**Ion Exchange-controlled Drug Release**

![Dextromethorphan Structure](image)

**Delsym 12 Hour Cough Relief**

---

By: Louis A. Bloomfield
Department of Physics, University of Virginia
Author of How Things Work: The Physics of Everyday Life
Evolution of Drug Delivery Systems

Drug Delivery Routes

Oral Delivery: <1 min ~ > 1 day

Localized Delivery: 1 month ~ 1 year

Transdermal: 1 day ~ 1 week

I.V. Infusion ~ 1 day

Implants (IM, SQ): 1 month ~ 1 year
Oral Controlled Drug Delivery Systems
**Highly Successful Oral Sustained Release Formulations**

12-hour delivery, 24-hour delivery

---

**TABLE 19.1 Examples of Branded Extended Release Products with Associated Patent Claims**

<table>
<thead>
<tr>
<th>Brand Product</th>
<th>Generic Name</th>
<th>Patent(s)</th>
<th>Claim Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall XR®</td>
<td>Amphetamine salts</td>
<td>US 6,322,819</td>
<td>FPK</td>
</tr>
<tr>
<td>Biaxin® XL</td>
<td>Clarithromycin</td>
<td>US 6,605300</td>
<td>FPK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6,010,718</td>
<td>FPK</td>
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<tr>
<td></td>
<td></td>
<td>US 6,551,616</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6,872,407</td>
<td>PK</td>
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<tr>
<td>Concerta®</td>
<td>Methylphenidate</td>
<td>US 6,919,373</td>
<td>PK</td>
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<tr>
<td></td>
<td></td>
<td>US 6,930,129</td>
<td>PK</td>
</tr>
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<td>Depakote® ER</td>
<td>Divalproëx</td>
<td>US 6,419,953</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6,511,678</td>
<td>FPK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6,528,090</td>
<td>FPK</td>
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<tr>
<td>Ditropan® XL</td>
<td>Oxybutynin</td>
<td>US 6,124,355</td>
<td>PK</td>
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<tr>
<td>Effexor® XR</td>
<td>Venlafaxine</td>
<td>US 6,274,171</td>
<td>F, FPK</td>
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<td></td>
<td></td>
<td>US 6,403,120</td>
<td>PK, FPK</td>
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<td></td>
<td></td>
<td>US 6,419,958</td>
<td>PK</td>
</tr>
<tr>
<td>Glucophage® XR</td>
<td>Metformin</td>
<td>US 6,475,521</td>
<td>F, FPK</td>
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<tr>
<td>Niaspan®</td>
<td>Niacin</td>
<td>US 6,406,715</td>
<td>PK</td>
</tr>
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<td></td>
<td></td>
<td>US 6,676,967</td>
<td>PK</td>
</tr>
<tr>
<td>Toprol® XL</td>
<td>Metoprolol</td>
<td>US 5,001,161</td>
<td>F</td>
</tr>
<tr>
<td>Wellbutrin® XL</td>
<td>Bupropion</td>
<td>US 6,096,341</td>
<td>FPK</td>
</tr>
</tbody>
</table>

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Need for Formulations of Poorly-Soluble Drugs

THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

A. Solubility

The solubility class boundary is based on the highest strength of an IR product that is the subject of a bio waiver request. A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media within the pH range of 1 - 6.8 at 37 ± 1°C. The volume estimate of 250 mL is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with an 8 fluid ounce glass of water.

B. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans, and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, other systems capable of predicting the extent of drug absorption in humans can be used (e.g., in situ animal, in vitro epithelial cell culture methods). A drug substance is considered to be highly permeable when the systemic BA or the extent of absorption in humans is determined to be 85 percent or more of an administered dose based on a mass balance determination (along with evidence showing stability of the drug in the GI tract) or in comparison to an intravenous reference dose.

C. Dissolution

An IR drug product is considered rapidly dissolving when a mean of 85 percent or more of the labeled amount of the drug substance dissolves within 30 minutes, using United States Pharmacopeia (USP) Apparatus 1 at 100 rpm or Apparatus 2 at 50 rpm (or at 75 rpm when appropriately justified (see section III.C.) in a volume of 500 mL or less (or 900 mL when appropriately justified) in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

An IR product is considered very rapidly dissolving when a mean of 85 percent or more of the labeled amount of the drug substance dissolves within 15 minutes, using the above mentioned conditions.

The BCS is used to set drug product dissolution standards to reduce the in vivo bioequivalence (BE) requirements.

Poorly Soluble Drugs: Amorphous Solid Dispersion

Table 2. List of commercial solid dispersions.

<table>
<thead>
<tr>
<th>Products</th>
<th>Drugs</th>
<th>Polymers</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afiditab®</td>
<td>Nifedipine</td>
<td>Poloxamer or PVP</td>
<td>Elan Corp, Ireland</td>
</tr>
<tr>
<td>Cesamet®</td>
<td>Nabipone</td>
<td>PVP</td>
<td>Lilly, USA</td>
</tr>
<tr>
<td>Cesamet®</td>
<td>Nabipone</td>
<td>PVP</td>
<td>Valeant Pharmaceuticals, Canada</td>
</tr>
<tr>
<td>Certican®</td>
<td>Everolimus</td>
<td>HPMC</td>
<td>Novartis, Switzerland</td>
</tr>
<tr>
<td>Gris-PEG®</td>
<td>Griseofulvin</td>
<td>PEG</td>
<td>Novartis, Switzerland</td>
</tr>
<tr>
<td>Gris-PEG®</td>
<td>Griseofulvin</td>
<td>PVP</td>
<td>VIP Pharma, Denmark</td>
</tr>
<tr>
<td>Fenoglide®</td>
<td>Fenofibrate</td>
<td>PEG</td>
<td>LifeCycle Pharma, Denmark</td>
</tr>
<tr>
<td>Nivadin®</td>
<td>Nivaldinipen</td>
<td>HPC/HPMC</td>
<td>Fujisawa Pharmaceuticals Co., Ltd</td>
</tr>
<tr>
<td>Nimotop®</td>
<td>Nimodipine</td>
<td>PEG</td>
<td>Bayer</td>
</tr>
<tr>
<td>Torcetrapib®</td>
<td>Torcetrapib</td>
<td>HPMC AS</td>
<td>Pfizer, USA</td>
</tr>
<tr>
<td>Ibuprofen®</td>
<td>Ibuprofen</td>
<td>Various</td>
<td>Seligs, USA</td>
</tr>
<tr>
<td>Incivek®</td>
<td>Telaprevir</td>
<td>HPMC AS</td>
<td>Vertex</td>
</tr>
<tr>
<td>Sponarox®</td>
<td>Itraconazole</td>
<td>HPMC</td>
<td>Janssen Pharmaceutica, Belgium</td>
</tr>
<tr>
<td>Omner®</td>
<td>Itraconazole</td>
<td>HPMC</td>
<td>Stiefel</td>
</tr>
<tr>
<td>Prograf®</td>
<td>Tacrolimus</td>
<td>HPMC</td>
<td>Fujisawa Pharmaceuticals Co., Ltd</td>
</tr>
<tr>
<td>Cymbalta®</td>
<td>Duloxetine</td>
<td>HPMC AS</td>
<td>Lilly, USA</td>
</tr>
<tr>
<td>Novxifil®</td>
<td>Posaconazole</td>
<td>HPMC AS</td>
<td>Merck</td>
</tr>
<tr>
<td>LCP-Tacro®</td>
<td>Tacrolimus</td>
<td>HPMC</td>
<td>LifeCycle Pharma, Denmark</td>
</tr>
<tr>
<td>Intellence®</td>
<td>Etravirine</td>
<td>HPMC</td>
<td>Tibotec, Yardley, PA</td>
</tr>
<tr>
<td>Incivo®</td>
<td>Etravirine</td>
<td>HPMC</td>
<td>Janssen Pharmaceuticals, Belgium</td>
</tr>
<tr>
<td>Resulmin®</td>
<td>Troglitazone</td>
<td>PVP</td>
<td>Pfizer, USA</td>
</tr>
<tr>
<td>Isoptin SRE-240®</td>
<td>Verapamil</td>
<td>Various</td>
<td>Seligs, USA</td>
</tr>
<tr>
<td>Isoptin SRE-240®</td>
<td>Verapamil</td>
<td>HPC/HPMC</td>
<td>Abbott Laboratories, USA</td>
</tr>
<tr>
<td>Creostor®</td>
<td>Rosuvastatin</td>
<td>HPMC</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Zelboraf®</td>
<td>Vemurafenib</td>
<td>HPMC AS</td>
<td>Roche</td>
</tr>
<tr>
<td>Zortress®</td>
<td>Everolimus</td>
<td>HPMC</td>
<td>Novartis, Switzerland</td>
</tr>
<tr>
<td>Kalydeco®</td>
<td>Ixacaflor</td>
<td>HPMC AS</td>
<td>Vertex</td>
</tr>
<tr>
<td>Kaletra®</td>
<td>Lopinavir and Ritonavir</td>
<td>PVP/polyvinyl acetate</td>
<td>Abbott Laboratories, USA</td>
</tr>
</tbody>
</table>

PVP: polyvinylpyrrolidone; HPMC: hydroxypropylmethylcellulose; PEG: polyethylene glycol; HPC: hydroxypropylcellulose; HMPC AS: hydroxypropylmethylcellulose acetylsuccinate.

Tran 2019, Overview of the manufacturing methods of solid dispersion technology for improving the solubility of poorly water-soluble drugs
Poorly Soluble Drugs: Amorphous Solid Dispersion

<table>
<thead>
<tr>
<th>Anticancer Drugs</th>
<th>Carriers</th>
<th>Methods</th>
<th>Attributes of Modified Anticancer Drugs</th>
<th>Reference</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicalutamide</td>
<td>PVP K30</td>
<td>Solvent evaporation</td>
<td>Using PVP K30 as carrier; SD showed the highest cumulative released percentage (about 98%) during the initial 10 min and stability after 6 months</td>
<td>[134]</td>
<td>2006</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>HPMC, PEG</td>
<td>Solvent evaporation</td>
<td>The solubility and dissolution of crystallized SD of docetaxel at 2 h were 34.2- and 12.7-fold higher, respectively, compared to the pure conventional drug</td>
<td>[78]</td>
<td>2011</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Poloxamer 188, PVP</td>
<td>Freeze-drying</td>
<td>A combination of poloxamer 188 and PVP in the preparation of docetaxel SD not only enhanced solubility, but also improved intestinal permeation</td>
<td>[135]</td>
<td>2016</td>
</tr>
<tr>
<td>Etoposide</td>
<td>PEG</td>
<td>Fusion method</td>
<td>The solubility and dissolution of etoposide in SD were higher in comparison with etoposide alone</td>
<td>[136]</td>
<td>1993</td>
</tr>
<tr>
<td>Etoposide</td>
<td>HPMC</td>
<td>Co-precipitation</td>
<td>At a ratio of drug to HPMC (1:1.5), drug release from SD was 75%, after 30 min, thereby improving oral absorption of etoposide</td>
<td>[137]</td>
<td>2014</td>
</tr>
<tr>
<td>Eosinomycin</td>
<td>Eudragit® RS05/sodium deoxycholate</td>
<td>Freeze-drying</td>
<td>The dissolution of SD showed a 46-fold increase in absorptive transport compared to the pure drug. In addition, AUC_{0-24h} of eosinomycin SD was 2.5-fold higher in comparison with that of drug alone</td>
<td>[138]</td>
<td>2017</td>
</tr>
<tr>
<td>Fluorometholide</td>
<td>PVP K30, PEG, Poloxamer 188</td>
<td>Lyophilization</td>
<td>The dissolution of fluorometholide was higher (85.68%) than the drug alone (13.45%) using poloxamer 188 as a carrier</td>
<td>[77]</td>
<td>2010</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Soluplus, polysorbate 188</td>
<td>Solvent evaporation, hot-melt extrusion</td>
<td>Solubility and dissolution of lapatinib SD were enhanced compared to the drug alone. After 15 min, the drug in SD was released at 92% compared to the drug alone (48%)</td>
<td>[78]</td>
<td>2018</td>
</tr>
<tr>
<td>Letrozole</td>
<td>CO2-menthol</td>
<td>Supercritical fluid</td>
<td>Solubility of letrozole SD using supercritical fluid in 7.1 times higher compared to that of the conventional drug</td>
<td>[139]</td>
<td>2018</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>HPMC, Ribo sugar ester L369</td>
<td>Supercritical fluid</td>
<td>The SD with drug, HPMC, Ribo sugar ester L369 ratio of 1:2.1 showed over 95% rapid dissolution within 30 min. In addition, AUC and C_{max} (24h) of drug in SD were 4.8- and 5.5-fold higher, respectively, compared to those in pure drug</td>
<td>[140]</td>
<td>2015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticancer Drugs</th>
<th>Carriers</th>
<th>Methods</th>
<th>Attributes of Modified Anticancer Drugs</th>
<th>Reference</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oridonin</td>
<td>PVP K17</td>
<td>Supercritical fluid</td>
<td>The dissolution of oridonin SD significantly increased compared to the original drug. In addition, the absorption of oridonin in SD showed 26.4-fold improvement in BA</td>
<td>[141]</td>
<td>2011</td>
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<tr>
<td>Paclitaxel</td>
<td>Poloxamer 188, PEG</td>
<td>Fusion method</td>
<td>Paclitaxel SD was successfully prepared, and the drug release from SD was higher than that of the drug alone</td>
<td>[86]</td>
<td>2013</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>HPMC AS</td>
<td>Solvent method</td>
<td>The solubility and permeability of paclitaxel were not increased simultaneously through supersaturation in vivo</td>
<td>[133]</td>
<td>2018</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>HP-β-CD, PEG, PVP, PEG 4000, MNT, SMP, Cremophor</td>
<td>Solvent evaporation, melting method, kneading method</td>
<td>The in vitro dissolution of prednisolone SD was improved compared with the pure drug</td>
<td>[87]</td>
<td>2011</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>PVP K30</td>
<td>Spray-drying</td>
<td>The absorption of raloxifene from SD showed 2.6-fold enhanced BA in comparison with the conventional drug</td>
<td>[142]</td>
<td>2013</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Soluplus</td>
<td>Spray-drying</td>
<td>The C_{max} and AUC_{0-48h} of sorafenib in SD formulation increased 1.5- and 1.8-fold, respectively, compared with the pure drug</td>
<td>[143]</td>
<td>2015</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Soluplus</td>
<td>Hot-melt extrusion</td>
<td>The dissolution and BA of tamoxifen in SD were improved compared with the drug alone</td>
<td>[105]</td>
<td>2018</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>HPMC AS</td>
<td>Solvent-controlled precipitation</td>
<td>The BA of vemurafenib in SD was improved 4-5-fold compared to the conventional drug</td>
<td>[144]</td>
<td>2013</td>
</tr>
</tbody>
</table>

HP-β-CD: hydroxypropyl-β-cyclodextrin; MNT: mannitol; SMP: skimmed milk powder.
PVP: polyvinylpyrrolidone; HPMC: hydroxypropylmethylcellulose; PEG: polyethylene glycol; HPC: hydroxypropylcellulose; HMPC AS: hydroxypropylmethylcellulose acetylsuccinate.

Tran 2019, Overview of the manufacturing methods of solid dispersion technology for improving the solubility of poorly water-soluble drugs.
Oral Delivery of Poorly-Soluble Drugs

Nanostructured lipid carriers (NLCs) | Solid lipid Nanoparticles (SLNs) | Self emulsifying formulations | Lipid nanocapsules

Layersomes | Liposomes | Emulsified lipids | Liposomes

Paracellular absorption | Uptake by M cells | Inhibition of P-gp | Fluid Phase Macropinocytosis

Phospholipids | Cholesterol | Mixed micelles

M-cell | Enterocytes | Lymphatic absorption

Macrophage | Systemic circulation

Physicochemical properties of drugs
- Intrinsic solubility
- Permeability
- Stability

Biological barriers
- Gastrointestinal transit time
- Absorption window
- Transmembrane efflux of drugs
- Pre-systemic metabolism

Limited oral bioavailability of drugs

Fig. 11. Absorption mechanisms implemented by lipidic nanocarriers for improving the oral bioavailability of drug substances.

Fig. 2. Schematic representation of the various challenges to the oral delivery of drugs.

Oral delivery of anticancer drugs: Challenges and opportunities.
Solubilization Methods for Poorly-Soluble Drugs

Manipulating Solubility by Changing

<table>
<thead>
<tr>
<th>Solid state properties</th>
<th>Solute-solvent interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size</td>
<td>pH control</td>
</tr>
<tr>
<td>Polymorphs</td>
<td>Ionic additives</td>
</tr>
<tr>
<td>Solvates</td>
<td>Co-solvents</td>
</tr>
<tr>
<td>Amorphous forms</td>
<td>Surfactants</td>
</tr>
<tr>
<td></td>
<td>Complexation</td>
</tr>
<tr>
<td></td>
<td>Polymer micelles</td>
</tr>
<tr>
<td></td>
<td>Hydrotropes</td>
</tr>
</tbody>
</table>

Each solubilization method has advantages and limitations.
Nanocrystal Formulations in Clinical Use

1. Rapamune (sirolimus, Wyeth 2000)
2. Emend (aprepitant, Merck 2003)
3. TriCor (fenofibrate, Abbott 2004)
4. Megace (megestrol acetate, Par 2005)
5. Triglide (fenofibrate, Skye Pharma 2005)
6. Invega Sustenna (paliperidone palmitate, Janssen 2009)

...their routine use in current marketed products. So far, only six commercial products, namely Rapamune (sirolimus, former Wyeth), Emend (aprepitant, Merck), TriCor (fenofibrate, Abbott), Megace (megestrol acetate, Par Pharmaceutical), Invega Sustenna (paliperidone palmitate, Janssen) and Triglide (fenofibrate, Skye Pharma) have resulted from nanocrystal technology [14] and approximately ten solid dispersion...

Oral Extended release formulations

Spheroidal Oral DAS  Programmable Oral DAS  Dual Release DAS

Intestinal Protective DAS  MatriX Drug Absorption System

Chronotherapeutic Oral DAS  BID.
Hydrophilic matrix-forming polymers

DAS: Drug Absorption System

Seroquel (Quetiapine)
AstraZeneca: $5 Billion
Depressive disorder
Nanocrystals for Improving Oral Bioavailability of Drugs

Review article
Nanosizing techniques for improving bioavailability of drugs
Raida Al-Kassas*, Mahima Bansal, John Shaw
School of Pharmacy, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

Bottom-Up Approach
Top-Down Approach

Wyeth 2000
Merck 2003
Abbott 2004
Par 2005
Skye Pharma 2005
Janssen 2009

Remote control devices

Scientific American. August 2010
Oral Delivery: Gastric Retention Devices

Hwang 1998, Gastric retentive drug delivery systems

FIGURE 5. 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).

FIGURE 6. Emulsion of the hydrodynamically balanced system (HBS). Diffusion of the gastric fluid into a droplet HBS system results in formation of the gelled polymer layer. Drug is released by diffusion and erosion of the gel barrier.

FIGURE 7. 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 float. From Ichikawa.19

FIGURE 8. settlement of a high-density device to the bottom of the stomach.

FIGURE 9. Attachment of a mucoadhesive dosage form to the mucosa layer in the stomach.

FIGURE 10. Interaction between polyelectrolyte and mucoadhesive molecules through numerous hydrogen bonding.

FIGURE 11. Mucoadhesive strength of polycarbophil to rabbit gastric tissue as a function of pH. From Park and Robinson.20

FIGURE 12. The system with the coiled arm (left) can unfold the arms (right) in the stomach. The expansion bar is expected to result in gastric retention. From Carminati and Co.21

FIGURE 13. The spherical form of the device is compacted (arrow in the left figure) for evacuation (center). In the stomach, the partially expanded form (right) is retained for extended gastric residence. From Caldwell et al.22

FIGURE 14. The expandable device can swell in the stomach either by absorbing water from the gastric juice or by evaporation of solidified or liquefied gas present in the device.

FIGURE 15. An example of an expandable device based on gas evaporation. The expanded device will be deflated upon removal of the plug by biodegradation. From Michaels et al.23

FIGURE 16. A dried superabsorbent hydrogel swells to a huge size in the stomach (A). As the drug is released, the swollen hydrogel can undergo degradation (B) and eventually is excreted from the stomach (E).

FIGURE 17. A dried superabsorbent hydrogel swells to a huge size in the stomach (A). As the drug is released, the swollen hydrogel can undergo degradation (B) and eventually is excreted from the stomach (E).

FIGURE 18. A sequence showing the movement of a swollen hydrogel to the pylorus by gastric contractions and retroperistalsis back to the body of the stomach as visualized by ultrasound and fluoroscopic imaging. From Shalaby et al.24
Oral Delivery: Gastric Retention Devices

Babaee 2019, Temperature-responsive biometamaterials for gastrointestinal applications

**In vivo temperature testing**

The temperature in the esophagus and stomach during administration of warm water was measured in a large animal model (three Yorkshire pigs).
Oral Peptide Delivery System

Rybelsus: building on 30 years of innovation

Understanding the mechanism of SNAC-enabled semaglutide absorption

Novo Nordisk selected Emisphere’s Eligen technology—in particular the SNAC absorption enhancer—for further development, even so later buying some of Merrion’s intellectual property in 2015 [13]. Emisphere had already clinically evaluated the site of absorption of an orally delivered peptide—evaluating their 4-CNAB absorption enhancer to enable delivery of oral insulin, comparing the absorption when the payload was delivered either to the stomach or the small intestine. The results that showed an improved glucose lowering effect from an immediate release tablet which delivered the payload to the stomach compared to delivery direct to the small intestine, an early indication that this might be a potential site of absorption for an orally delivered peptide. This was a surprising finding as the prevailing dogma at the time was that oral peptides should target the small intestine [14].

Lewis 2022, Development and approval of rybelsus (oral semaglutide)
Victor 2014, Eligen technology for oral delivery of proteins and peptides
**Oral Delivery: Biotherapeutics**

**Fig. 1**: RP design. a) Fully assembled enteric-coated RP. b) Schematic drawing showing various parts and components of the RP. Inset shows the microsyringe containing the needle with the drug microparticle which gets injected into the jejunal wall. The microparticle and needle are aseptically manufactured in an isolator and hermetically sealed inside a drug chamber which is then inserted in the microsyringe.

**Fig. 5**: PK of octreotide in healthy human volunteers. a) Time-course of changes in plasma concentrations of octreotide delivered via RP A and B. b) Time-course of changes in plasma octreotide levels following octreotide administration either IV (N=6) or orally via the RP (N=13, groups A and B combined) in healthy human volunteers. Numbers in the table below the graphs are PK parameters for the IV and RP groups. Data are presented as means \pm SE.

<table>
<thead>
<tr>
<th>Group</th>
<th>(C_{\text{max}}) (ng/mL)</th>
<th>(T_{\text{max}}) (min)</th>
<th>AUC (_{\text{last}/\text{Dose}}) (\text{ng*min/mL)/(µg/kg)}</th>
<th>Bioavailability (% F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Sandostatin (N=6)</td>
<td>11.1 ± 1.6</td>
<td>5</td>
<td>389 ± 22</td>
<td>NA</td>
</tr>
<tr>
<td>RP (N=13)</td>
<td>2.4 ± 0.3</td>
<td>50</td>
<td>226 ± 30</td>
<td>65 ± 9</td>
</tr>
</tbody>
</table>

Dhalla 2022, A robotic pill for oral delivery of biotherapeutics
Opioid Use Disorder & Purdue Pharma

Judge Overturns Purdue Pharma’s Opioid Settlement
The ruling said the company’s owners, members of the Sackler family, could not receive protection from civil lawsuits in return for a $4.5 billion contribution.

Suing the suppliers
Here’s a look at the states that have filed lawsuits against opioid manufacturers in the wake of the nationwide opioid crisis.

Purdue Pharma is NOT related to Purdue University
Opioid Use Disorder & Abuse-Deterrent Formulations

COVID-19 disrupts efforts to address the opioid epidemic.

When we provide treatment, we talk about relapse triggers. I'm hard-pressed to think of a bigger relapse trigger than what we're going through now as a country.

Park 2019, Prevention of opioid abuse and treatment of opioid addiction- Current status and future possibilities

Number and age-adjusted rates of drug overdose deaths by state, US 2019


Various ways of abusing opioid formulations in capsule and tablet forms. Current opioid formulations, including abuse-deterrent formulations, can be easily manipulated into powders for abuse by smoking, snorting, and chewing. These powders can be further treated with water or organic solvents to extract opioids for intravenous injection.

Figure 1

Approaches to abuse deterrence used in opioid drug formulations. Opioid formulations can be prepared in microparticles to deter physical manipulations of dosage forms and/or by adding a gelling agent to hinder opioid extraction. To hinder abuse by smoking, snorting, or chewing, certain agents causing a foul order or a burning sensation can be added, along with agents causing nausea or emesis. An opioid antagonist such as naloxone or naltrexone can be sequestered in a formulation that can be released only if tampered with.

Figure 2

[Diagram showing various ways to abuse opioid formulations and different methods to prevent abuse.]
Transdermal Drug Delivery Systems
Transdermal Drug Delivery Systems

Fig. 1 Cross-sectional view of several TDS: (a) pressure-sensitive adhesive (PSA) matrix device; (b) membrane-moderated TDS; (c) adhesive-controlled TDS; (d) microreservoir-type TDS; (e) matrix dispersion-type TDS.


PLGA Nanofibers for Transdermal Delivery

Fig. 4. Schematic figure of cross-sectional view of D-NLCs-Azone-nanofibers.

PLGA Nanofibers for Transdermal Delivery

Fig. 5. In vitro release profile of daidzein from D-NLCs-Nanofibers and D-NLCs-Azone-Nanofibers in Phosphate Buffered Saline (pH 7.4). Keys: (▲) D-NLCs- Nanofibers, (■) D-NLCs-Azone-Nanofibers. Each value represents the mean±SD (n = 3).

Transdermal Patches with Microneedles

Microneedle Transdermal Drug Delivery

Phase-Transition Microneedle Patches

A) The microneedles absorb the bodily fluid from the dermis layer to convert form hard glassy state to hydrogel state to allow the preloaded insulin to release to the bodily fluid in the dermis layer.

B) The microneedle matrix of PTM is cross-linked to avoid dissolution through microcrystalline domains as the cross-linking junctions via a freeze-thaw treatment while that of HFM is cross-linked through covalent bands as the cross-linking junctions via a chemical reaction. Therefore, insulin can be loaded in the needle tips of PTM to achieve a relative bioavailability of 20%, while insulin has to be loaded at the back of the microneedle array of HFMs that leads to a bioavailability less than 1% due to the extended diffusion pathway.


Fig. 2 Schematic illustration of the design of PVP MN arrays containing pH-responsive PLGA HMs and their mechanism for codelivery of two different model drugs Alexa 488 and Cy5 in sequence transdermally. After insertion into skin, the first step of rapid release of Alexa 488 and Dil-labeled HMs was accomplished due to quick

Polymeric Microneedles for Transdermal Protein Delivery

Fig. 1. Representative types of polymeric MNs for protein delivery. A) Solid MNs coated with polymeric drug formulation on the MNs surface for direct delivery. B) Dissolvable polymeric MNs that remain in the skin and dissolve to deliver the drug encapsulated within. C) Degradable polymeric MNs that remain in the skin and degrade over time. Drug delivery occurs via passive diffusion or degradation of the polymeric matrix. D) Bioreponsive polymeric MNs. Drug release is dependent on the degradation or dissociation of MN matrix and/or formulations from the MN matrix.

Poly(lactic-co-glycolic acid) Gradient Porous Microneedle Array


Fig. 6. (a) GPMA loaded with dried Rhodamine B at microneedle tips, (b) rabbit skin punctured by GPMA, and (c) drug diffusion image of punctured skin slice.

Fig. 7. Transdermal insulin delivery in diabetic rats: (a) diabetic SD rats with a weight of approximately 200 ± 20 g were selected, (b) SD rat treated with GPMA patch, (c-d) skin recovery process after removing the GPMA, and (e) BGLs in diabetic rats after transdermal administration of insulin-loaded GPMA and SC injection (n=5).
Transdermal Vaccine Patches

Vaccine Patch: Vaccination without needles, the best idea ever

Medicinal Patches

At China's Chengdu University of Traditional Chinese Medicine hospital, twin sisters Zheng Yue and Zheng Hao wear medicinal patches that contain a formula of herbal medicine used as a seasonal treatment to expel heat from the body during summer. Photograph by Fritz Hoffmann. Nat Geo 2019: A Year in Review
Long-Acting Drug Delivery Systems
Dimensions of Drug Delivery Systems

- **Micro Drug Vehicles**
  - Size: 100 μm

- **Nano Drug Vehicles**
  - Size: 10 μm

- **Virus**
  - Size: 1 μm

- **Proteins & DNA**
  - Size: 100 nm

- **Drug Molecules**
  - Size: 10 nm

- **Atoms**
  - Size: 1 nm

- **Size:**
  - 100 nm
  - 10 μm
  - 1 μm
  - 10 nm
  - 1 nm
  - 0.1 nm
FIGURE 1 Mechanisms of therapeutic polymers.
1. Intravenous polymer conjugates or nanoparticles control drug pharmacokinetics;
2. Sub-cutaneous polymer depot formulation controls delivery of active moiety;
3. Soluble oral polymer drugs neutralize infective or immunogenic agents in GI tract;
4. Insoluble, orally-active polymer sequestrant causes fecal removal of undesired agents;
5. Polymer drugs act as blood bulking agents or in vivo surfactants;
6. Polymer drugs act as topical anti-infectives.

Connor 2017, Polymers as drugs
Methods for Making Nano/Micro Particle


   - Non solvent (polymer soluble in organic solvent)
   - Salting-out (polymer soluble in water)
   - Calcium
   - Tripolyphosphates

   Method based on physico-chemical properties of polymer solutions
   - Phase
   - Gelation

   POLYMER

2. Atomization methods
   - Spray drying
   - Spray freeze-drying
   - Ultrasonic atomization
   - Electrospray

3. Nano/micro fabrication

   Method derived from microencapsulation techniques
   - Emulsification
     - Simple Emulsion W/O (water soluble)
     - Simple Emulsion O/W (polymer soluble in organic solvent)
     - Double Emulsion W/O/W (polymer soluble in organic solvent)

   - Gelation
     - Solvent evaporation
     - Solvent extraction
     - Inverse salting out
     - Solvent evaporation

   - Polymer precipitation
     - Nanospheres
     - Nanoparticles
     - Nanocapsules

Fig. 3 Summary of the different methods to prepare nanospheres and nanocapsules from a polymer. W/O: water-in-oil, O/W: oil-in-water, W/O/W: water-in-oil-in-water.

Double Emulsion Methods for Microparticle Preparation

Small Hydrophobic Drugs

Hydrophobic Drug (●) in Organic Solvent 1 (O₁)

PLGA in Organic Solvent 2 (O₂) → O₂/O₂ Emulsion → O₂/O₂/W Double Emulsion → Drying

Peptide and Protein Drugs

Protein (●) in Aqueous Solution (W)

PLGA in Organic Solvent (O) → W/O Emulsion → W/O/W Double Emulsion
Pharmacokinetic Profiles of Long-Acting Formulations

**Nutropin Depot™**
Somatotropin (rDNA origin) for injectable suspension

**Trelstar Suspension™**
Somatotropin (rDNA origin) for injectable suspension

- **Nutropin Depot™**
  - Single dose mean GH concentration in pediatric GHD patients
  - **C<sub>max</sub>** = 40 ng/mL in 3 hours

- **Trelstar Suspension™**
  - **C<sub>max</sub>** = 36 ng/mL in 4 hours
Injectable Long-Acting Formulations Approved by the FDA

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lupron Depot</strong> (leuprolide acetate for depot suspension)</td>
<td>1, 3, 4, 6 months, MP 1989, 1996, 1997, 2011 7.5 mg/month</td>
</tr>
<tr>
<td><strong>Trelstar</strong> (tripotassium desmopressin for injection)</td>
<td>1, 3, 6 months, MP 2000, 2001, 2010 3.75 mg/month</td>
</tr>
<tr>
<td><strong>Vivitrol</strong> (naltrexone for extended-release injectable suspension)</td>
<td>1 month MP, 2006 380 mg/month</td>
</tr>
<tr>
<td><strong>Signifor LAR</strong> (pasireotide for injectable suspension)</td>
<td>1 month, MP, 2014 20, 40, 60 mg/month</td>
</tr>
<tr>
<td><strong>Somatulin LA</strong> (Lanreotide acetate)</td>
<td>1 month MP, 2017 22.5 mg/month</td>
</tr>
<tr>
<td><strong>Zoladex</strong> (goserelin acetate for depot suspension)</td>
<td>1, 3 months SI, 1989 3.6 mg/month</td>
</tr>
<tr>
<td><strong>Sandostatin LAR Depot</strong> (octreotide acetate for injectable suspension)</td>
<td>1 month MP, 1998 20 mg/month</td>
</tr>
<tr>
<td><strong>Arestin</strong> (minocycline HCl (mg MICROSPHERES)</td>
<td>2 weeks MP, 2001 1 mg/2 weeks</td>
</tr>
<tr>
<td><strong>Propel</strong></td>
<td>1 month SI, 2011 0.37 mg/month</td>
</tr>
<tr>
<td><strong>Zilretta</strong></td>
<td>3 months MP, 2017 32 mg/3 months</td>
</tr>
<tr>
<td><strong>Bydureon BCise</strong> (buprenorphine extended-release)</td>
<td>1 week MP, 2012, 2017 (BCise) 2 mg/week</td>
</tr>
<tr>
<td><strong>Lutrate Depot</strong> (Leuprolide acetate)</td>
<td>3 months MP, 2018 22.5 mg/month</td>
</tr>
<tr>
<td><strong>Scenesse</strong> (Afamelanotide Implant)</td>
<td>2 months SI, 2019 8 mg/month</td>
</tr>
<tr>
<td><strong>Durysta</strong> (bimatoprost implant)</td>
<td>4-6 months SI, 2020 10 μg/6 months</td>
</tr>
</tbody>
</table>

**Notes:**
- MP: Microparticle
- SI: Solid implant
- IS: In Situ forming implant
- **Discontinued**: Lutrate Depot (1999-2001)
Pharmacokinetic Profiles of Long-Acting Formulations

A. Eligard®

Pharmacokinetic/pharmacodynamic response.

Lupron®

Concentration-time profiles.

45 mg / 6 months
Issues with Delivery of Biopharmaceuticals

Protein Formulations

Proteins: Tertiary structures

Factors to consider for formulation:
- Loading capacity
- Encapsulation efficiency
- Release profiles → *In vitro & in vivo* correlation
- Protein stability → Bioactivity

Polymers: Biodegradable polymers

Scale-up production

Stability
Drug Delivery: Future
Precision Medicine

Pharmacogenetics
The study of genetic factors (heredity) that influence response to drugs and the predisposition to develop adverse effects. The correlation of the DNA sequence of genes to a drug response.

Pharmacogenomics
The implementation of large-scale genomic approaches to this question. The study of the pattern of expression of genes involved in a drug response in a defined environment.
Pirmohamed 2001, Pharmacogenetics and pharmacogenomics

Precision Medicine
“Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?” (B.H. Obama 2015. The precision medicine initiative. https://obamawhitehouse.archives.gov/precision-medicine).

Pharmacokinetics
How does this link to drug response? Well, pharmacogenomics considers whether the altered variant form of the protein is involved in either:

Pharmacodynamics
Every therapeutic that enters the body follows an identical process of absorption, distribution, metabolism and excretion (ADME) – but one that is specific to that drug.

Challenges in pharmacogenomics
- Quantifying the economic impact and cost-effectiveness of pharmacogenomic profiling
- Implementing next generation sequencing as a routine clinical measurement
- Distinguishing between functional driver mutations and non-functional mutations when selecting targeted therapies for pharmacological intervention

Pharmacokinetics refers to the sum of these processes.
<table>
<thead>
<tr>
<th>Delivery Technology</th>
<th>Formulation Barriers</th>
<th>Biological Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly water-soluble drug delivery</td>
<td>• New excipients for increasing drug solubility</td>
<td>• Non-toxic to the body</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No drug precipitation in the blood</td>
</tr>
<tr>
<td>Peptide/protein/nucleic acid delivery</td>
<td>• Control of drug release kinetics</td>
<td>• IVIVC</td>
</tr>
<tr>
<td></td>
<td>• Control of drug loading</td>
<td>• Long-term delivery up to a year</td>
</tr>
<tr>
<td></td>
<td>• Control of therapeutic period</td>
<td>• Non-invasive delivery</td>
</tr>
<tr>
<td>Targeted drug delivery using nanoparticles</td>
<td>• Control of nanoparticle size, shape, surface chemistry, functionality, and flexibility.</td>
<td>• Controlling biodistribution through altering vascular extravasation, renal clearance, metabolism, etc.</td>
</tr>
<tr>
<td></td>
<td>• Surface modification with ligands</td>
<td>• Navigating microenvironment of diseased tissues to reach target cells</td>
</tr>
<tr>
<td></td>
<td>• Stimuli-sensitive delivery systems</td>
<td>• Crossing endothelial barriers (e.g., blood-brain barrier)</td>
</tr>
<tr>
<td>Self-regulated drug delivery</td>
<td>• Signal specificity &amp; sensitivity</td>
<td>• Functional inside the body</td>
</tr>
<tr>
<td></td>
<td>• Fast responsive kinetics</td>
<td>• Functional over the lifetime of drug delivery</td>
</tr>
<tr>
<td></td>
<td>• Ability to stop drug release</td>
<td></td>
</tr>
</tbody>
</table>
Antibodies against PEG

Figure 12. Anti-PEG antibodies can destabilize pegylated liposomal doxorubicin. (A) Anti-PEG antibodies that bind to PEGylated liposomal doxorubicin (PLD) can activate complement and cause formation of a membrane attack complex (which forms a pore) in the liposomal membrane, breaking the internal salt and proton gradients. (B) Loss of the ammonium sulfate and proton gradients results in rapid dissolution of the doxorubicin nanocrystal and diffusion of drug from the liposomes. (C) Cryogenic electron microscopy image of PLD showing a single doxorubicin nanocrystal in each liposome. (D) Image of empty liposomes after incubation of PLD with anti-PEG IgG and complement. Arrows indicate the membrane attack complex.

Chen 2021, Polyethylene glycol immunogenicity- Theoretical, clinical, and practical aspects of anti-polyethylene glycol antibodies
Chhetri 2019, Cell culture and coculture for oncological research in appropriate microenvironments

In Vitro 3D Models Mimicking Human Physiology

Hemichannel model of breast cancer

Tumor-Microenvironment-on-chip

3D Mini-Guts

Figure 6 Coculture of non-neoplastic epithelial cells and cancer cells in the DOC. (A) Immunofluorescence image resulting from the staining of T4-2 tumors with dil prior to their seeding in the hemichannel. Non-neoplastic S1 cells were cultured on acrylic hemichannels covered with laminin 111 for 10 days to sustain their proliferation and differentiation. Tumor nodules (3 days old, prepared in 3D culture) were stained with dil (red) and seeded in the hemichannels for coculture with S1 cells. Cell nuclei were stained with DAPI (blue). Arrows point to areas with S1 cells only (this image is focused on the top of the hemichannel). (B) Image focused on the bottom portion of a hemichannel of the DOC containing only the monolayer of S1 cells. (C) Reconstituted hemichannel with 3D view based on the stacking of optical sections of the layer of S1 cells (shown using the 3D viewer of ImageJ; only the cells delineating the limits of the hemichannel in this image are shown). Size bar, 50 μm.

Chhetri 2019, Cell culture and coculture for oncological research in appropriate microenvironments

Ozcelikkale 2017, Differential response to doxorubicin in breast cancer subtypes simulated by a microfluidic tumor model

Immunocytochemical characterization of human colon organoids (Colon-87, SCC321). Human colon PDOs are positive for colon-specific markers: CA II, CA IV and Mucin5B, posterior hindgut marker: CDX2, stem cell markers: Lgr5 and Sca1 and epithelial markers: TPH-1 and E-Cad.

Fig. 1. Design and fabrication of T-MOC to simulate the drug transport at the TME. (A) Schematic of the fabricated T-MOC platform and its operating pressure conditions. Detailed 3D configuration of the device is illustrated in cross-sectional view – top layer with capillary channel, nanoporous membrane, and bottom layer with interstitial and lymphatic channels. This design is to mimic a pair of capillary-lymphatic vessels with tumor tissues. (B) 3D morphology of breast cancer cells grown on the T-MOC: MCF-7 and MDA-MB-231. Comparison of growth rate of MCF-7 and MDA-MB-231 under 2D culture and 3D T-MOC culture configurations.

Human large intestine tissue under a microscope.