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

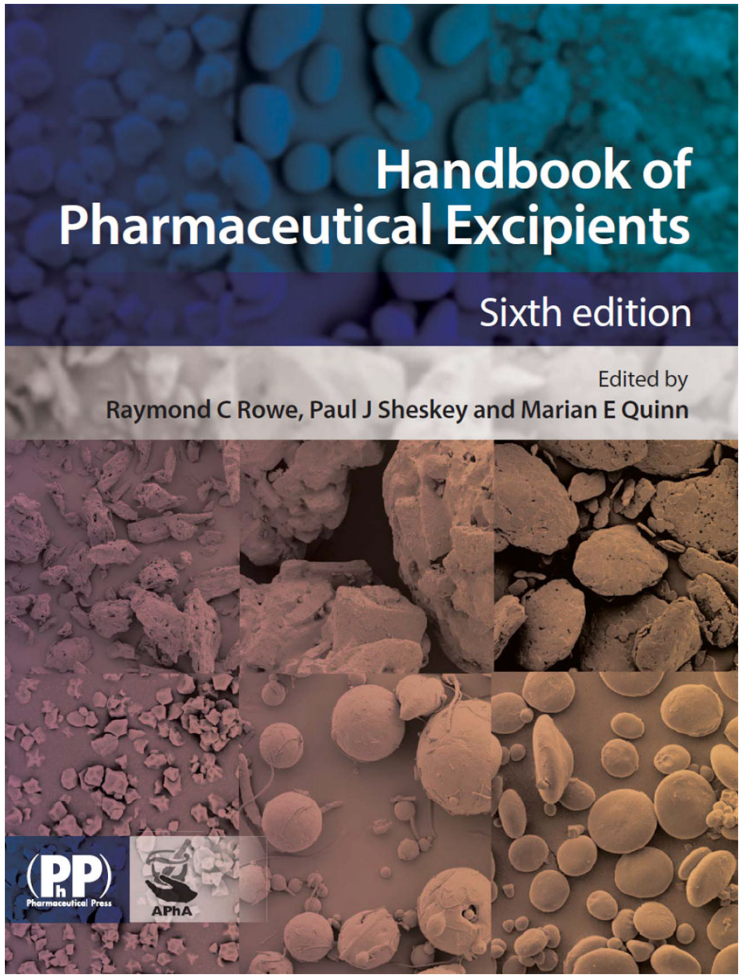
- Sustained-release Systems
- Extended-release Systems
- Delayed-release Systems
- Therapeutic Systems

Drug Delivery Systems = Drug + Everything Else (Excipients)

Excipients should be "generally regarded as safe (**GRAS**)" materials

Handbook of Pharmaceutical Excipients

Rowe 2009, Handbook of Pharmaceutical Excipients



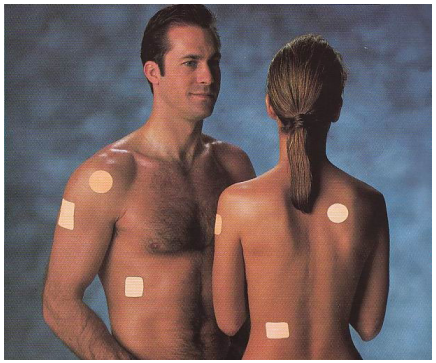
The book can be downloaded from the folder “7. Pharmaceutical Polymers”

Controlled Release Drug Delivery Systems

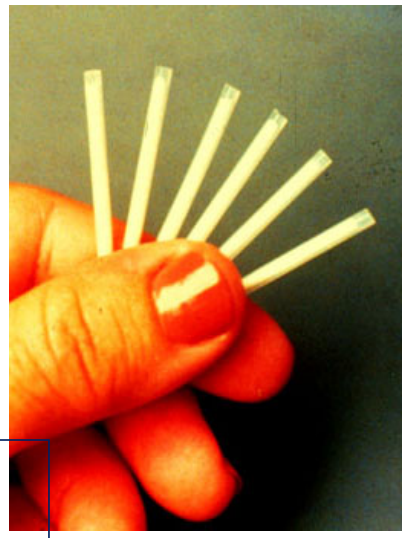
Controlled release, Sustained release, Extended release, Modified release, Programmed release

Long-Acting Systems: Less Frequent Administration → Improved patients' compliance & convenience

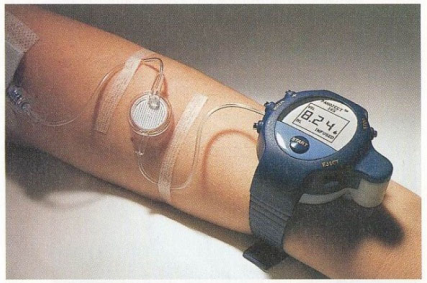
Once-a-day
Once-a-week



Once-a-month
Once-a-year



On-demand

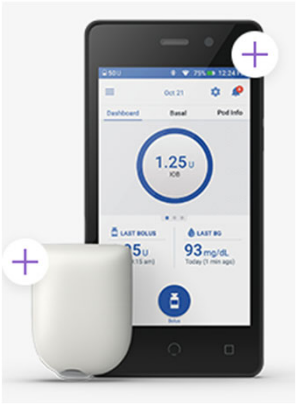


People using patient-controlled analgesia, such as the push-button Panoject (above), tend to give themselves smaller doses than they would receive in the every-four-hour system.

Norplant: Made of Silicone rubber
36 mg levonogestrel.
85 µg/day (later 30 µg/day) up to 7 years.

Disadvantages

Relatively high production cost
Dose dumping
Surgical operation
Difficulty in stopping drug release
Biocompatibility issue

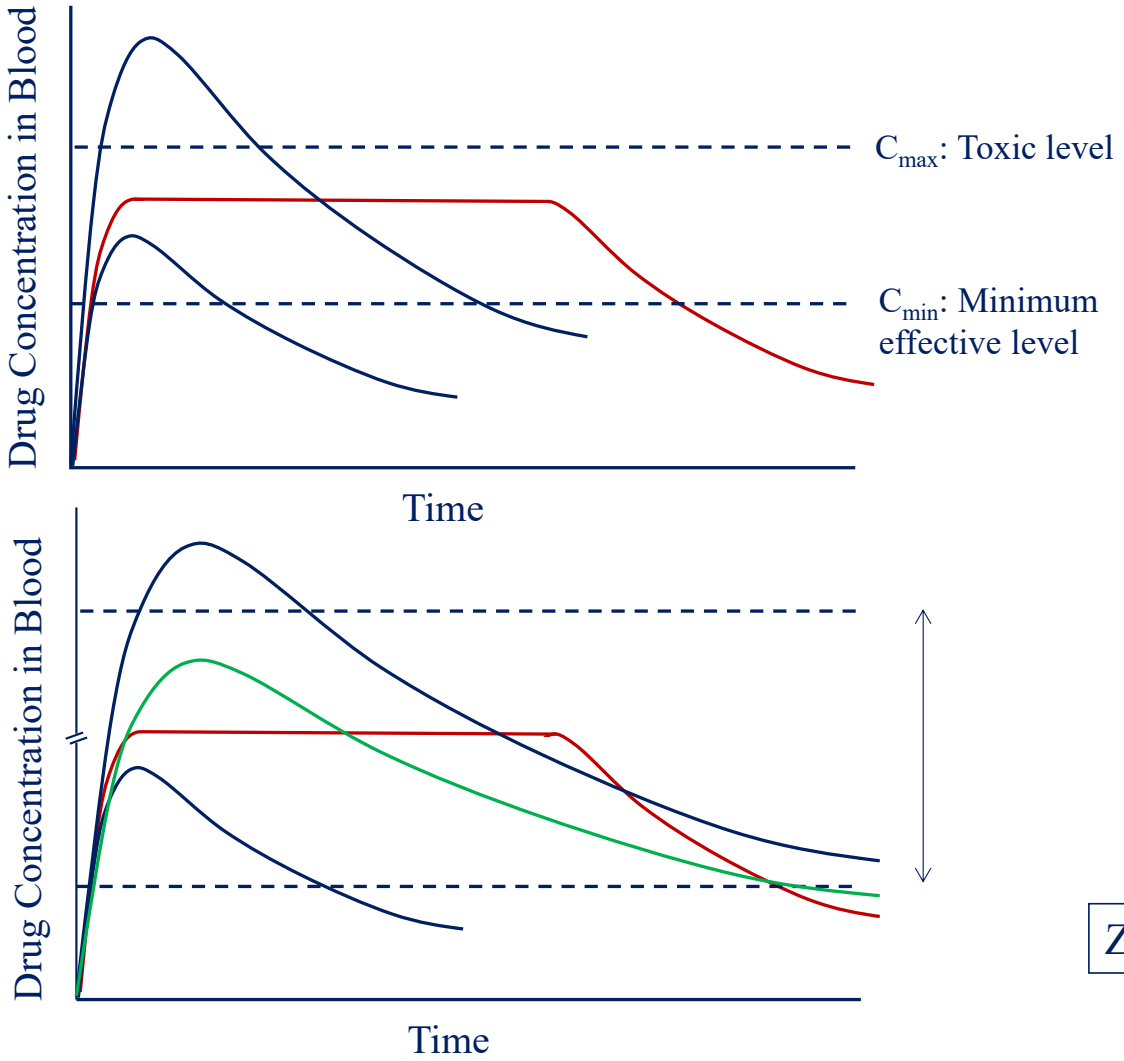


Discover Omnipod DASH®

A tubeless, wireless insulin management system that lets you experience more freedom with fewer daily hassles. Wear the Pod for 3 days (up to 72 hours) of continuous insulin delivery, without multiple daily injections. And the convenience doesn't stop there. Get it all through the pharmacy, with no commitment. Even the Personal Diabetes Manager (PDM) comes at no cost with your first box of Pods†.

https://www.omnipod.com/

Rationale of Controlled Drug Delivery Systems



Therapeutic Index (TI) = C_{max}/C_{min}

TI values of selected drugs

Drug	TI
Theophylline	∞
Triphenylamine	19,000
Diphenhydramine	2,300
Chlorpheniramine	1,400
Penicillin	>100
Acetaminophen	20-40
Barbiturates	2-7
Quinidine	2-3
Digitoxin	1.5

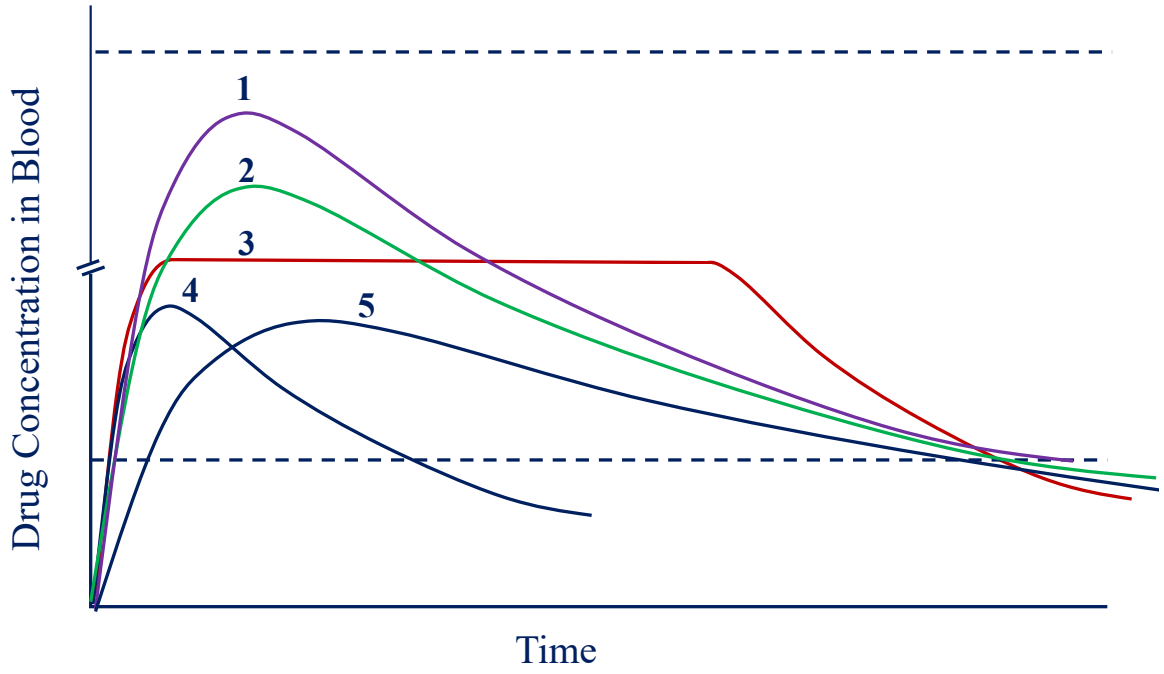
Candidate drugs for sustained release?

Zero-order release system?

Rationale of Controlled Drug Delivery Systems

Which of the following PK profiles is the best?

Theoretical answer vs. Practical answer

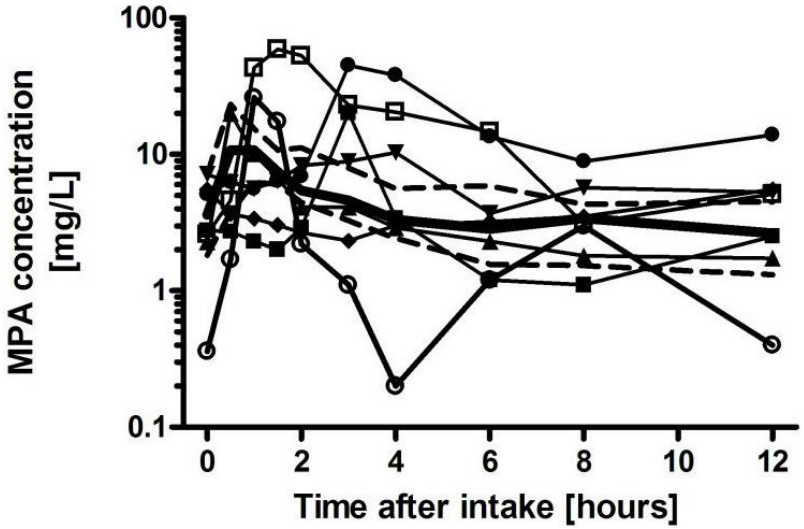


Consider how a new drug is tested and approved.

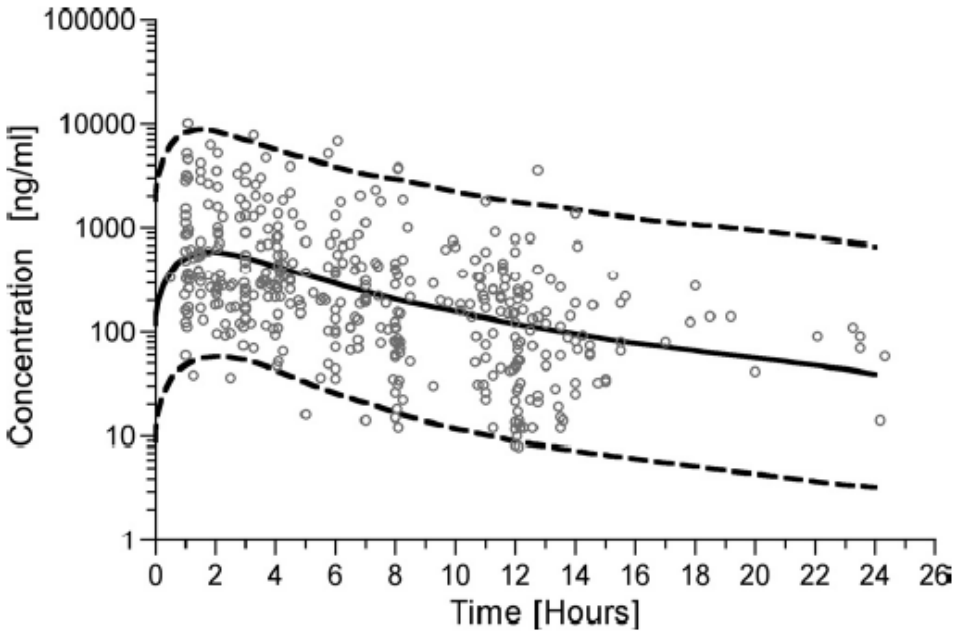
Consider what does personalized medicine mean.

Human Pharmacokinetic Variations

Any small difference in drug release behavior due to formulation changes may be insignificant.
The inter-individual variations are so significant that any small formulation changes are likely to be buried in the inter-individual variations.
Thus, the new formulation needs to be 10X better, not 100% (1X) better.



Patients on enteric-coated mycophenolate sodium (EC-MPS) showed random PK profiles (Figure 2). For the convenience of the reader, we superimposed the actual PK profiles over the percentiles of the mycophenolate mofetil profiles.
Six individual pharmacokinetic PK profiles of 6 pediatric patients with autoimmune disease on EC-MPS, superimposed on figure 1.
https://ped-rheum.biomedcentral.com/articles/10.1186/1546-0096-8-1



RAL concentrations (circles) versus time standardized for a 400-mg BID dosing in HIV and HIV individuals, with population predictions (solid line) and the 95% prediction interval (dashed lines)

Population Pharmacokinetic Analysis and Pharmacogenetics of Raltegravir in HIV-Positive and Healthy Individuals Arab-Alameddine et al. Antimicrobial Agents and Chemotherapy 56(6): 2959–2966, 2012.

Evolution of Controlled Drug Delivery Systems

1950 1960 1970 1980 1990 2000 2010 2020 2030

1952 Spansule®
Dissolution-control

1974 Ocusert®
Diffusion-control

1975 OROS®
Osmosis

1982 Delsym®
Ion exchange

1989 Lupron Depot®
PLGA Microparticle

Nanomedicine

1974 InFed®
Iron-Dextran Complex

1979 Transderm Scop®

1990 Norplant®
Implant

2000 Mylotarg™
Ab-Drug Conjugate

2000 Rapamune®
Nanocrystal

2019 Rebelsus®
Oral Peptide Tablet

Small Molecules

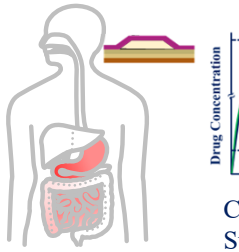
Peptide & Protein Drugs

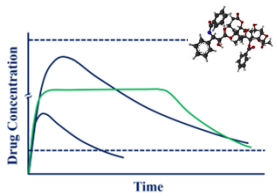
Targeting

Biological Barriers

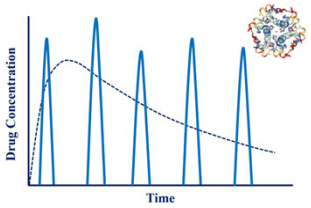
Long-Term Treatment

Basic Drug Delivery Mechanisms





Controlled release ≈ Sustained Release



Modulated drug delivery

Drug release kinetics controls pharmacokinetic (PK) profile → **Body controls PK profile**

1994 Taxol®
Paclitaxel in PEGylated Castor Oil

2005 Abraxane®
Paclitaxel-Albumin Complex

2018 Onpattro®
RNAi in PEGylated Lipid Nanoparticle

1990 Adagen®
PEGylated Protein

2014 Movantik
PEGylated naloxol

1964 Liposome (Bangosome)

1995 Doxil®
PEGylated Liposome

2017 Kymriah® CAR-T Gene Therapy

2021 Comirnaty®
PEGylated Lipid Nanoparticle

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

https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/part-iii-drugs-and-foods-under-1938-act-and-its-amendments

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."

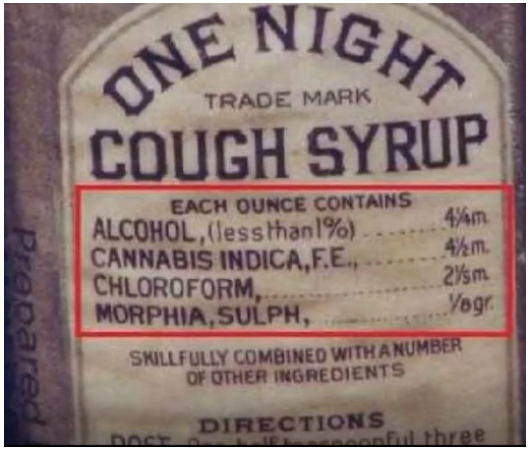
Thalidomide devastation

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

American Experience: The Poison Squad

'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).

https://www.pbs.org/video/the-poison-squad-5sf93j/

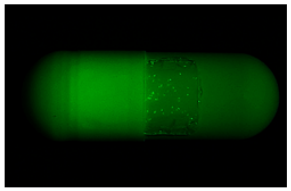
PurdueTODAY

January 28, 2020 Current web edition

ADDITIONAL NEWS

PBS show to feature work of one of Purdue's first faculty members

"The Poison Squad," a PBS documentary airing at 9 tonight (Jan. 28), tells the story of government chemist Dr. Harvey Wiley, one of Purdue's first chemistry professors and Indiana's first state chemist. Wiley worked to regulate the safety of food and drugs and is known as the "Father of the Pure Food and Drugs Act." In 1901, Wiley set out to prove Americans were being harmed by chemicals in food and organized volunteers for human trials to test the effects of chemical food preservatives.

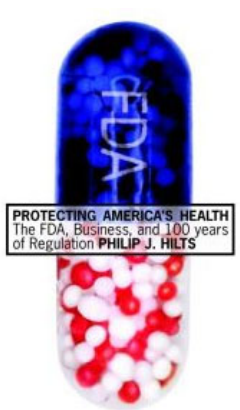


Edible 'security tag' to protect drugs from counterfeit

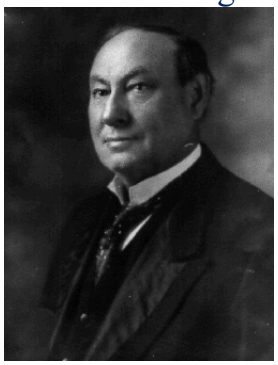
Manufacturing prescription drugs with distinct markings, colors, shapes or packaging isn't enough to protect them from counterfeiting, U.S. Drug Enforcement Administration reports have shown. Purdue researchers are aiming to stump counterfeiters with an edible "security tag" embedded into medicine. To imitate the drug, a counterfeiter would have to uncrack a complicated puzzle of patterns not fully visible to the naked eye.

The Food and Drug Administration (FDA)

Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation

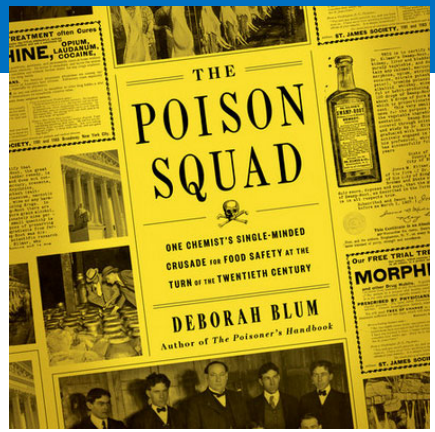


Philip J. Hilts. 2003



Dr. Harvey Washington Wiley: Creator of the FDA. Professor at Purdue University.

The Poison Squad: One Chemist's Single-Minded Crusade for Food Safety at the Turn of the Twentieth Century



"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/

Wiley and some of the first federal scientists of the Bureau of Chemistry (1906).

The first significant clinical study on the effect of food preservatives (1902). (No control group!)

The Jungle (1906)

Sinclair. "I aimed at the public's heart (workers' right), and by accident I hit it in the stomach."

Upton Sinclair : The Jungle

A NAUSEATING JOB, BUT IT MUST BE DONE
(President Roosevelt takes hold of the investigating muck-rake himself in the packing-house scandal.)

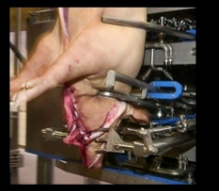
- The effects from the accusations against the meat packing industry in *The Jungle* led to investigations into the food and patent medicine industry in general.

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?



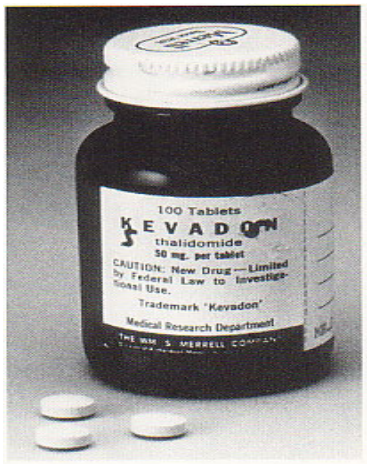
- *The Jungle's* fictitious characters tell of men falling into tanks in meatpacking plants and being ground up with animal parts, then made into "Durham's Pure Leaf Lard."
- Historian Stewart H. Holbrook argues this was nonsense. Sinclair's *The Jungle* was far from reality:
  - ***"The grunts, the 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."***

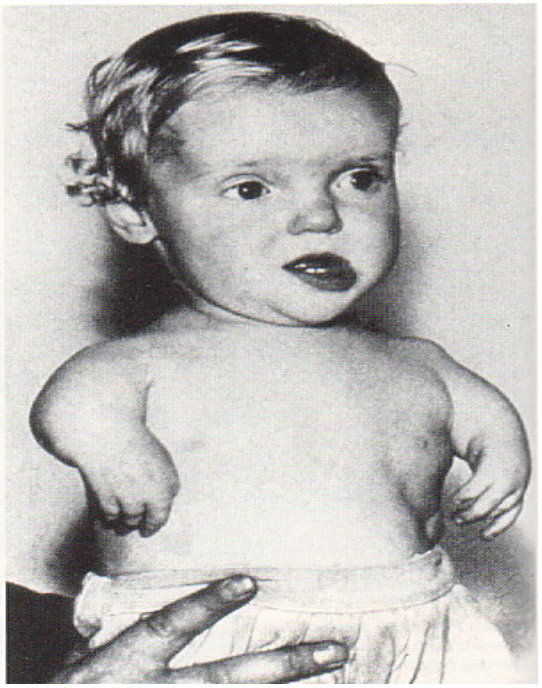
Criticism of Upton Sinclair's *The Jungle*

- When the sensational accusations of *The Jungle* became worldwide news, foreign purchases of American meat dropped by *HALF!* American meat packing companies were losing a huge market share.
- The meatpackers looked for new regulations to give their markets a calming sense of security so the public (and consumers across the world) would trust and buy their meat instead of fearing what was in it.
- Congressional hearings for what became the Meat Inspection Act of 1906 were held by Congressman James Wadsworth's Agriculture Committee:
- *"Knowing that a new law would allay public fears fanned by The Jungle, bring smaller competitors under regulation, and put a newly-laundered government stamp of approval on their products, the major meat packers strongly endorsed the proposed act and only argued over who should pay for it."*

https://www.slideshare.net/iRawrPanda/upton-sinclair-and-critics-of-the-jungle

The Thalidomide Incidence





Above: *Kevadon, also known as thalidomide. It was sold chiefly outside the United States as a sedative despite a lack of testing to determine if it was safe. It caused birth defects when taken in the early months of pregnancy, and led to thousands of cases of premature death and, most famously, a fetal disability in which limbs were stunted. The FDA refused to approve it without better safety data.*

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

Frances Kelsey:
Medical officer at FDA Refusal to allow NDA of thalidomide based on insufficient safety data.

History Repeats Itself

Different subjects but the same cycle:

Ignorance, Outrage, & New law protecting consumers

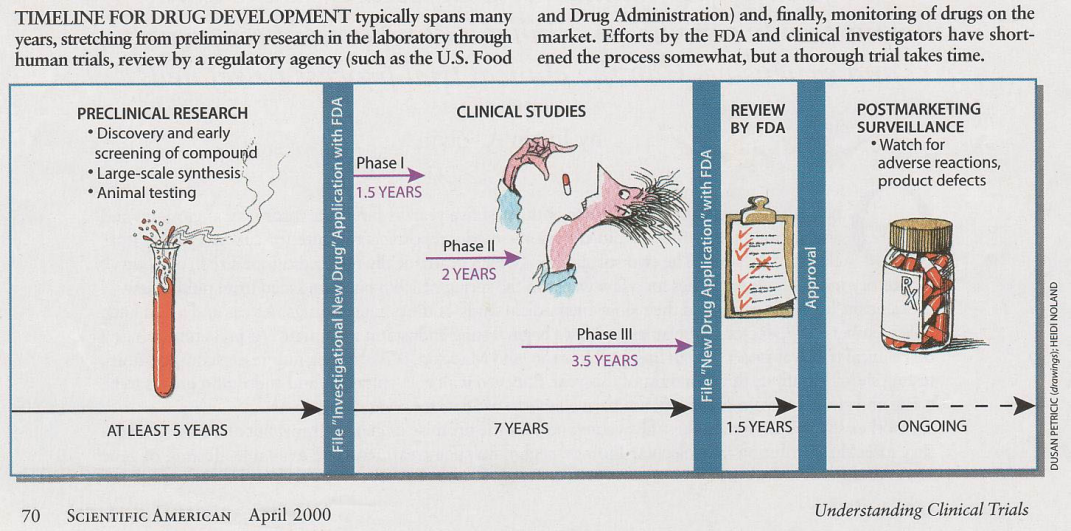
Industries for profit

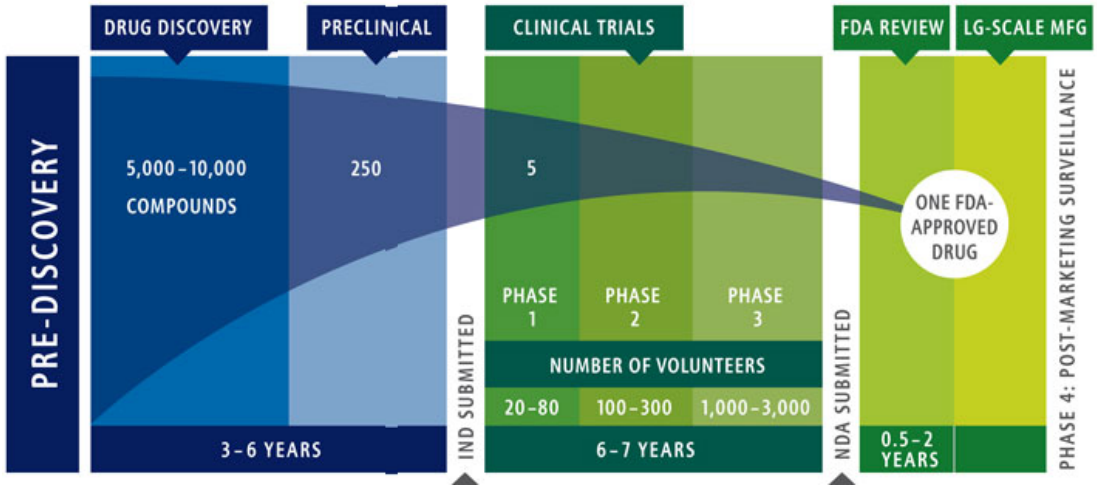
- **Food industry**
  - **Livestock (water consumption and methane (CH_4) emission)**
  - **Fishery & Fishing industry**
- **Tobacco industry**
- **Opioid pain killers**
- **Plastics industry**
- -
- -
- -

The Danger of Hypes: History rhymes

Importance of the Food & Drug Administration

Safety and Efficacy of Drug Delivery Systems





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

Source: PhRMA adaption based on Tufts Center for Study of Drug Development (CSDD) Briefing: Cost of developing a new drug. Nov. 2014. Tufts CSDD & School of Medicine and US FDA Infographic.
Drug Approval Process: http://www.fda.gov/downloads/Drugs/ResourcesForYou/consumers/UCM284393.pdf
http://www.phrma.org/advocacy/research-development/clinical-trials
https://publicpolicy.wharton.upenn.edu/live/news/1764-debate-over-the-priority-review-voucher/for-students/blog/news.php

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 State.

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.

2 **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.

http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm295473.htm

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 in this phase 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.

FDA Drug Approval Process

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.

PDUFA
Prescription Drug User Fee Act

Since the PDUFA was passed in 1992, more than 1,000 drugs and biologics have come to the market, including new medicines to treat cancer, AIDS, cardiovascular disease, and life-threatening infections.

PDUFA has enabled the Food and Drug Administration to bring access to new drugs as fast or faster than anywhere in the world, all while maintaining the same thorough review process. Under PDUFA, drug companies agree to pay fees that boost FDA resources, and FDA agrees to time frames for its review of new drug applications.

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
(http://www.nbcnews.com/storyline/ebola-virus-outbreak/ebola-drug-zmapp-gets-fda-fast-track-n429156)
(https://www.statnews.com/2016/10/12/ebola-zmapp-trial-results/)
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 Deevelopment

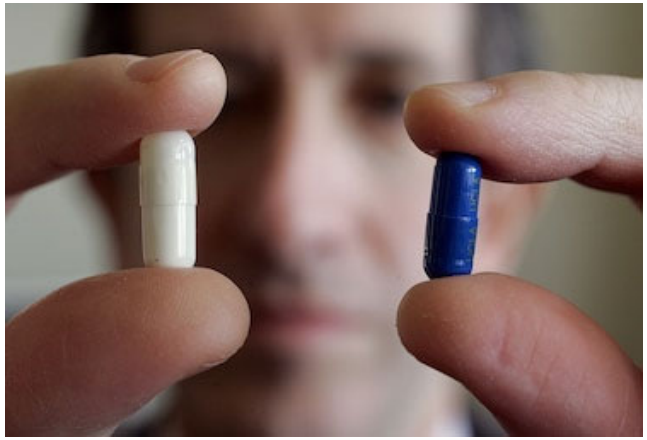
POST-MARKETING: FDA's Post-Approval Risk Assessment Systems

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

Clinical Studies: Efficacy Better Than Placebo

Most of the trials done so far on open-label placebos have been small, but the results are starting to add up. A systematic review published last year in Scientific Reports evaluated 13 studies with nearly 800 participants and concluded that open-label placebos exhibit significant positive effects. The reviewers cautioned, though, that in the early stages of research in any field, positive studies are more likely to be published than those not supporting the technique. Still, the unexpected effect has many medical experts intrigued.



The use of placebos in clinical trials really took off in the 1960s, after Congress passed an amendment that authorized the U.S. Food and Drug Administration to require pharmaceutical companies to prove that new drugs were not just safe but also effective. Clinical trials comparing a medicine to a harmless placebo became the accepted way to do that, scientists noted in the New England Journal of Medicine on the amendments' 50th anniversary.
In traditional clinical trials, participants are never informed whether they are receiving the drug or the placebo. Scientists evaluating the trial data are not told either, so the results are supposed to be more directly comparable and less likely to introduce bias.

The fact that it's prescribed by a physician is also key, experts say. "A placebo isn't about the pill. It's the ritual of the pill," Kaptchuk says.

"This is not about believing you're going to get better," Kaptchuk surmises. "In my opinion, this is about the body knowing something that's not conscious."

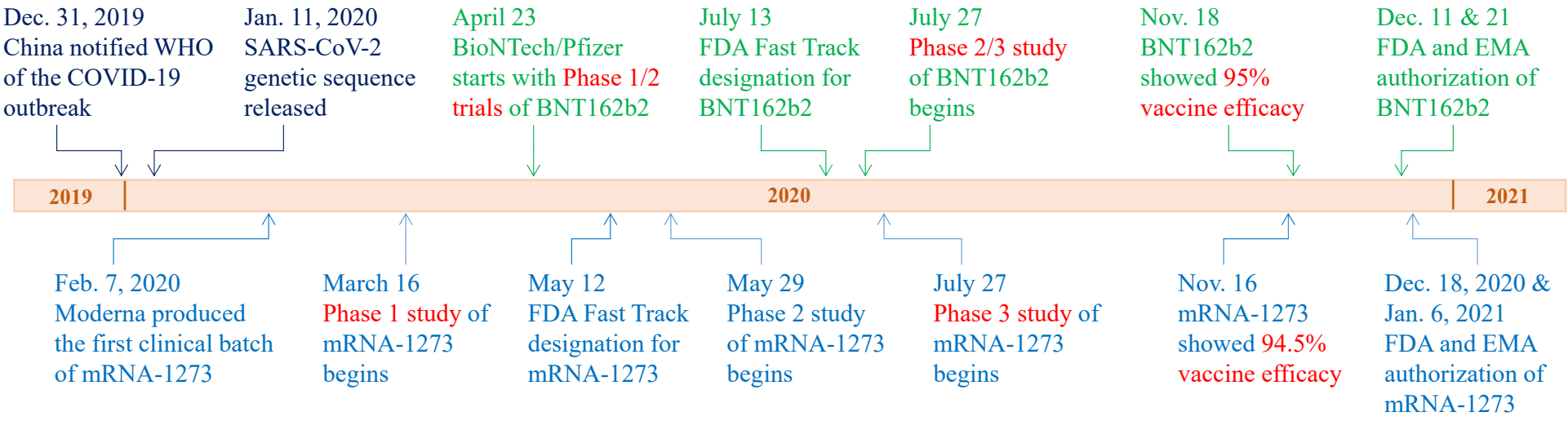
"The mind plays such an important role in patient recovery," Krystal says. Like all placebos, open-label ones take advantage of the bond between doctors and patients that is "one of the most special and unique connections among people in our society."

Landau 2022, Why a placebo can work—even when you know it's fake

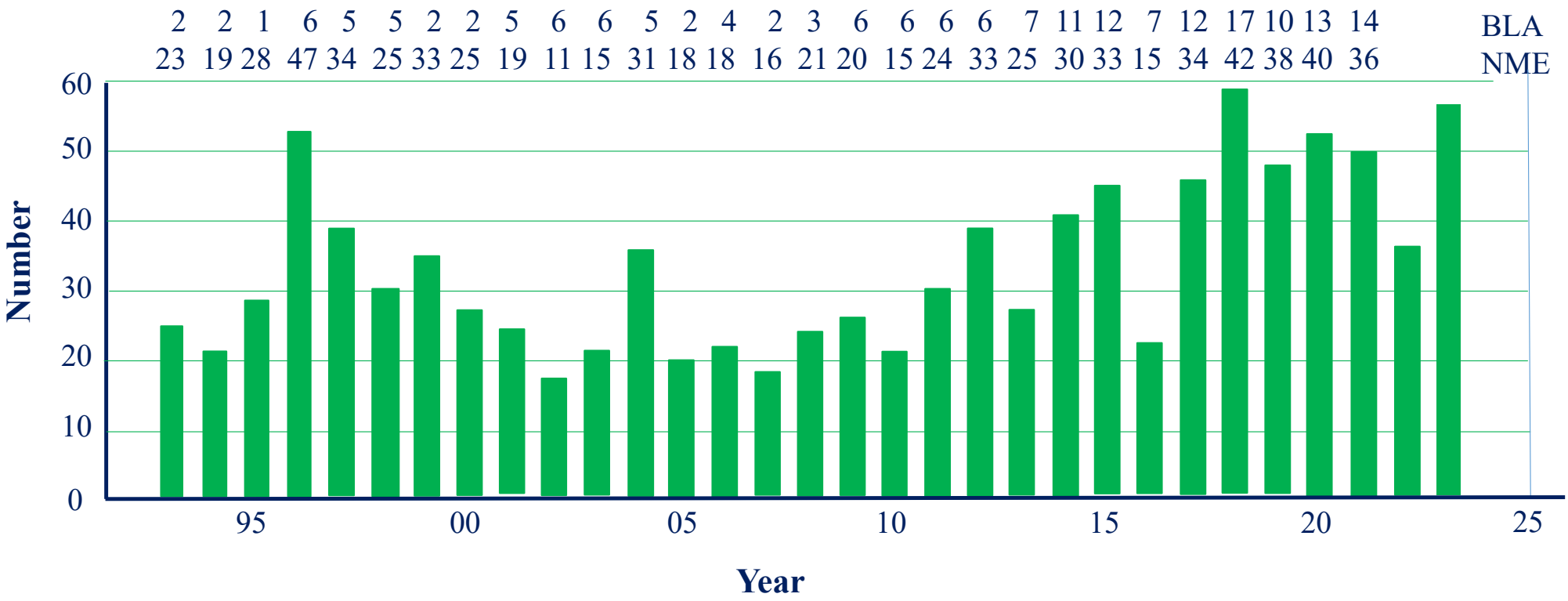
https://www.nationalgeographic.com/magazine/article/why-a-placebo-can-workeven-when-you-know-its-fake?rid=FF526C1F1B0738788B420FE1D0034350&cmpid=org%3Dngp%3A%3Amc%3Dcrm-email%3A%3Asrc%3Dngp%3A%3Acmp%3Deditorial%3A%3Aadd%3DHealth_20220925&loggedin=true

Clinical Studies are Essential for Safety and Efficacy

COVID-19 Vaccine Development



FDA Approvals of Novel Drugs



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

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm
https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm592464.htm

http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm295473.htm
https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2021

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

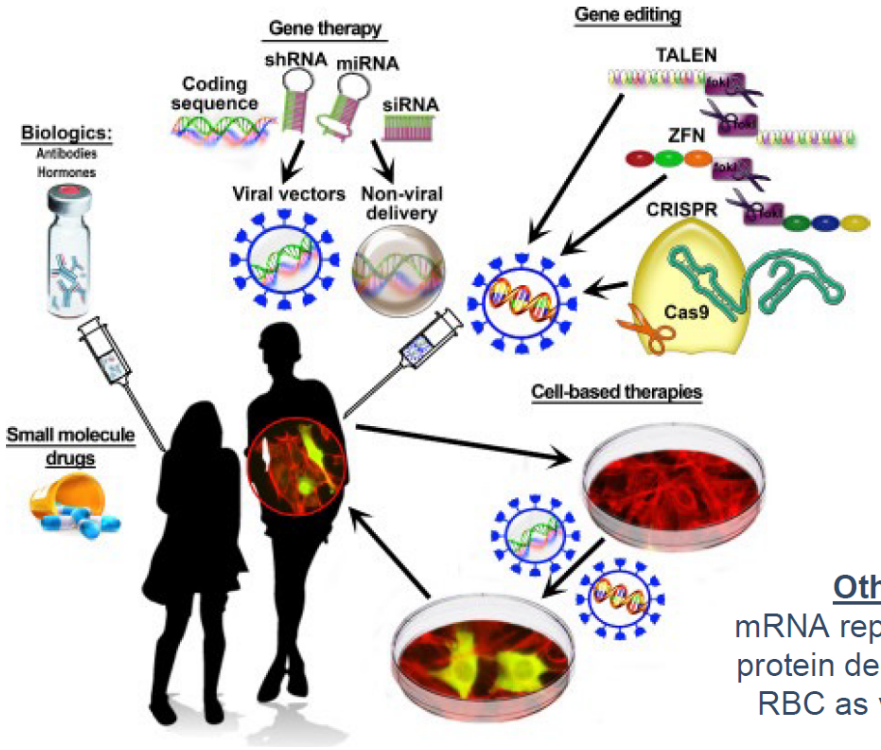
No human phenotype for drug efficacy testing

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

Trial and Error Approach



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

Alzheimer's Disease

Science and technology

The Economist July 25th 2015

Dementia

Flattening the slope

A glimmer of hope in the fight against a dreadful illness

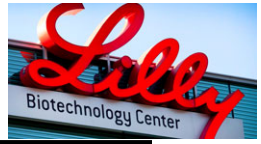
ALZHEIMER'S disease is incurable, and only barely treatable. Drugs such as Aricept bring temporary relief, but nothing halts its onward march. There was therefore a lot of excitement, among researchers and journalists alike, in the lead-up to a lecture given on July 22nd at the Alzheimer's Association 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.

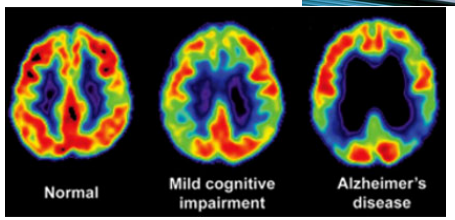
Their something is an antibody, called solanezumab by its inventors, that sticks to beta amyloid. This is one of the proteins which contribute to the plaques and tangles of matter in the brain that are characteristic of the disease. The researchers hoped, when they began the study, that solanezumab might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

When Lilly tested the drug in 2012, 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. ■





https://www.nytimes.com/2016/11/23/health/eli-lillys-experimental-alzheimers-drug-failed-in-large-trial.html?_r=0

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-Cog_{14} (Alzheimer's Disease Assessment Scale-Cognitive subscale). https://investor.lilly.com/releasedetail.cfm?ReleaseID=1000871

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

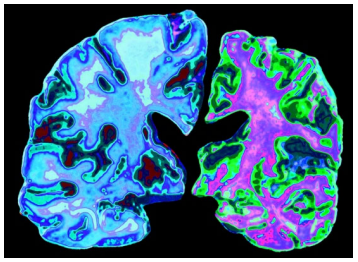
http://www.alzforum.org/therapeutics/solanezumab

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



Brain of healthy 70-year-old (left) compared with brain of 70-year-old with Alzheimer's (right).

http://www.nature.com/news/failed-alzheimer-s-trial-does-not-kill-leading-theory-of-disease-1.21045

Merck Scraps Disappointing Experimental Cholesterol Drug

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.

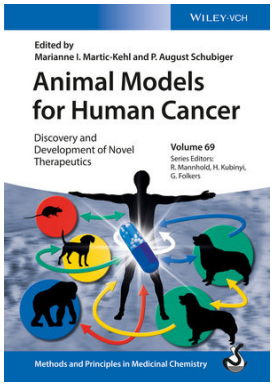
Georgetown University cardiologist Dr. Allen J. Taylor said he thinks the drug would be approved by the Food and Drug Administration despite its "relatively weak benefit."
"If you were discussing this with patients," Taylor said, "you would have to tell them that when you start this, you'll have to take 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.

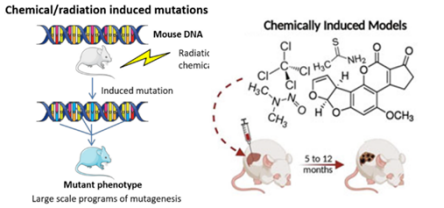
Linda A. Johnson. 10/12/2017

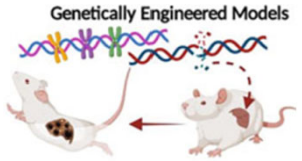
https://www.pharmpro.com/news/2017/10/merck-scraps-disappointing-experimental-cholesterol-drug?et_cid=6133840&et_rid=54728378&location=top&et_cid=6133840&et_rid=54728378&linkid=https%3a%2f%2fwww.pharmpro.com%2fnews%2f2017%2f10%2fmerck-scraps-disappointing-experimental-cholesterol-drug%3fet_cid%3d6133840%26et_rid%3d%%subscriberid%%%26location%3dtop

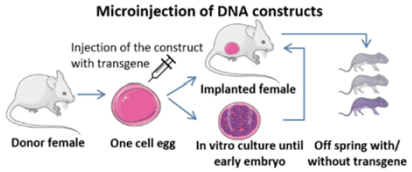
https://www.pharmpro.com/news/2017/08/new-drug-reduces-heart-attacks-enough?cmpid=horizontalcontent

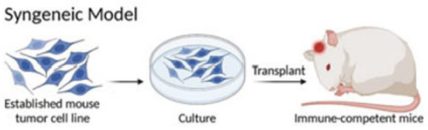
Animal Models for Cancer Studies

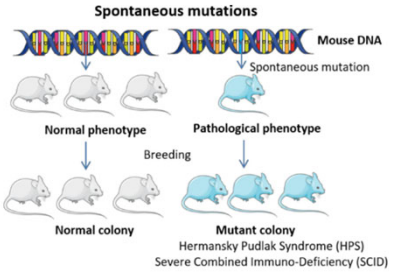


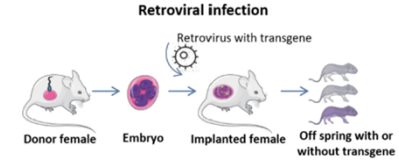


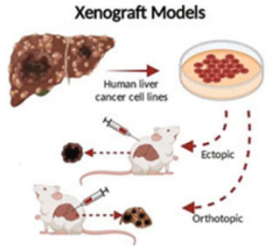


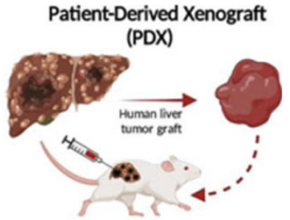








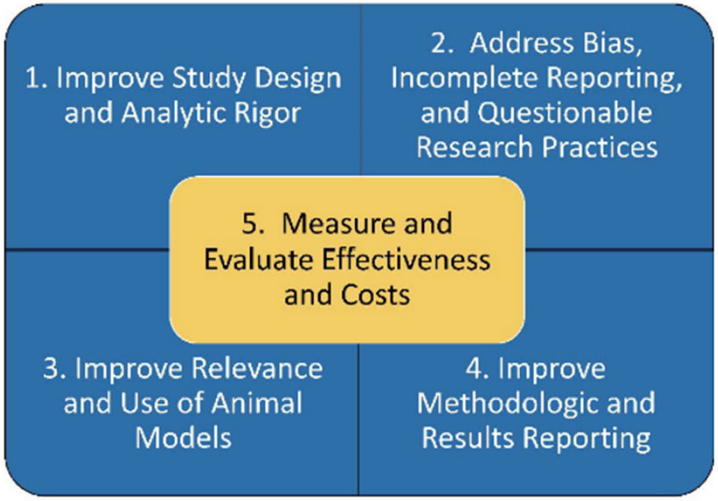




Commonly used animal models for cancer studies.
(Dhumal et al., Preclinical animal models for cancer research and drug discovery, in Bose & Chaudhari, Eds., Unravelling Cancer Signaling Pathways. 2019.)
https://www.eara.eu/why-are-animals-used-cancer-research

Das et al., Importance of animal models in the field of cancer research & Karakurt et al., Animal model of human cancer: malignant lymphoma/ colon cancer/lung cancer/liver cancer/brain tumors/skin cancer (in Pathak 2023, Handbook of Animal Models and its Uses in Cancer Research)

Animal Models



Improving the translatability of animal models

ACD Working Group on Enhancing Rigor, Transparency and Translatability in Animal Research Report, 2021

- Advised how NIH can help researchers improve rigor, transparency, and reproducibility of animal research
- Overarching goals
  - o Increase confidence in quality and applicability of research
  - o Ensure animal subjects used with consideration of ethics and harm-benefit analysis

NIH 2021, ACD working group on enhancing rigor, transparency, and translatability in animal research

Elaine A. Ostrander, Ph.D.
Chief & NIH Distinguished Investigator
Cancer Genetics and Comparative Genomics Branch

Definition: An animal model is a non-human species used in biomedical research because it can mimic aspects of **a biological process or disease** found in humans. Animal models (e.g., mice, rats, zebrafish and others) are sufficiently like humans in their anatomy, physiology or response to a pathogen that researchers can extrapolate the results of animal model studies to better understand human physiology and disease. By using animal models, researchers can **perform experiments that would be impractical or ethically prohibited with humans**. --- Overall, animal models have proven valuable in studies of nearly every human condition.

(https://www.genome.gov/genetics-glossary/Animal-Model#)

How to Improve Animal Models for Better Treatment?

It's Not the Animal Model, Inadequate.
It's the Human Use, Inadequate.

Much of the published animal data on nanomedicine is irrelevant to clinical translation.

- Our interpretation of the animal data is often too optimistic.
- Most animal data are presented in a highly positive way to increase their values.
- Only positive results of animal studies are published.
- One common manifestation of cancer nanomedicine is the use of saline solutions as a control.

Publishing negative results is very difficult, making animal models seemingly unsuitable for studying cancer nanomedicine.

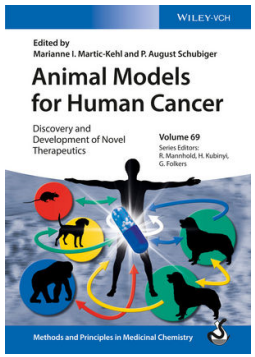
5

How to End Selective Reporting in Animal Research

Gerben ter Riet and Lex M. Bouter

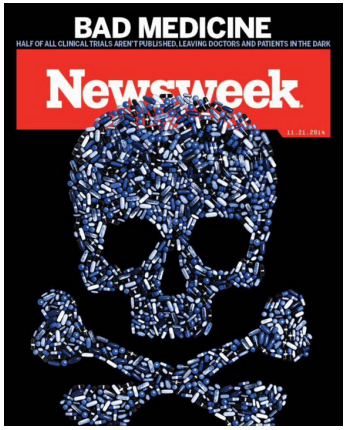
5.1 Introduction

Would scientific progress not be a lot swifter and cheaper if we published, in some convenient format, all results from our negative studies too? Although convincing evidence is not available, we think the answer would be affirmative. New empirical results appear daily, but it can sometimes take years for *knowledge* to emerge. Isolated studies may be important, but almost all deeper scientific insights evolve at the meta-level; that is, at the level of collections of similar studies around a particular scientific question. Since the 1980s, in clinical medicine and public health, systematic reviews (often including a meta-analysis) of the literature have been increasingly employed to produce ("meta-level") *knowledge* [1]. These systematic reviews ought to be updated when a new piece of evidence comes along. The crucial role of integration of new findings with existing ones is not always appreciated in animal experimental work, although its justification was eloquently expressed over a century ago:



How to End Selective Reporting in Animal Research
Gerben ter Riet and LexM. Bouter
(Martic-Kehl 2016, Animal Models for Human Cancer)

Clinical Study Results



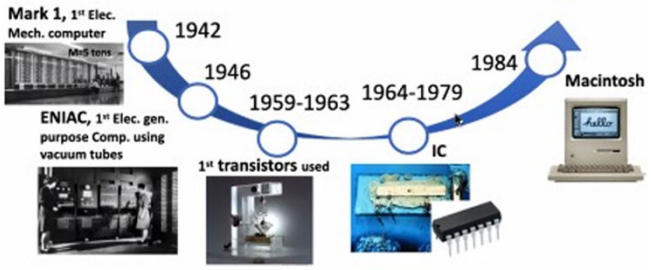
Newsweek. November 21, 2014

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.

Ryan Mandelbaum. Scientific American. January 2017

Slower Progress in New Drug Development



1964

UNIVAC 1108 (1 MB memory)

2021

Laptop
(32 GB memory)

1964 Liposome (Bangosome)

1990 Adagen®
ADAGEN® (pegademase bovine) Injection
PEGylated Protein

1994 Taxol®
Paclitaxel in PEGylated Castor Oil

2005 Abraxane®
Paclitaxel in Albumin Complex

1995 Doxil®
PEGylated Liposome

2014 Movantik
movantik® (naloxegol) Tablets
PEGylated naloxol

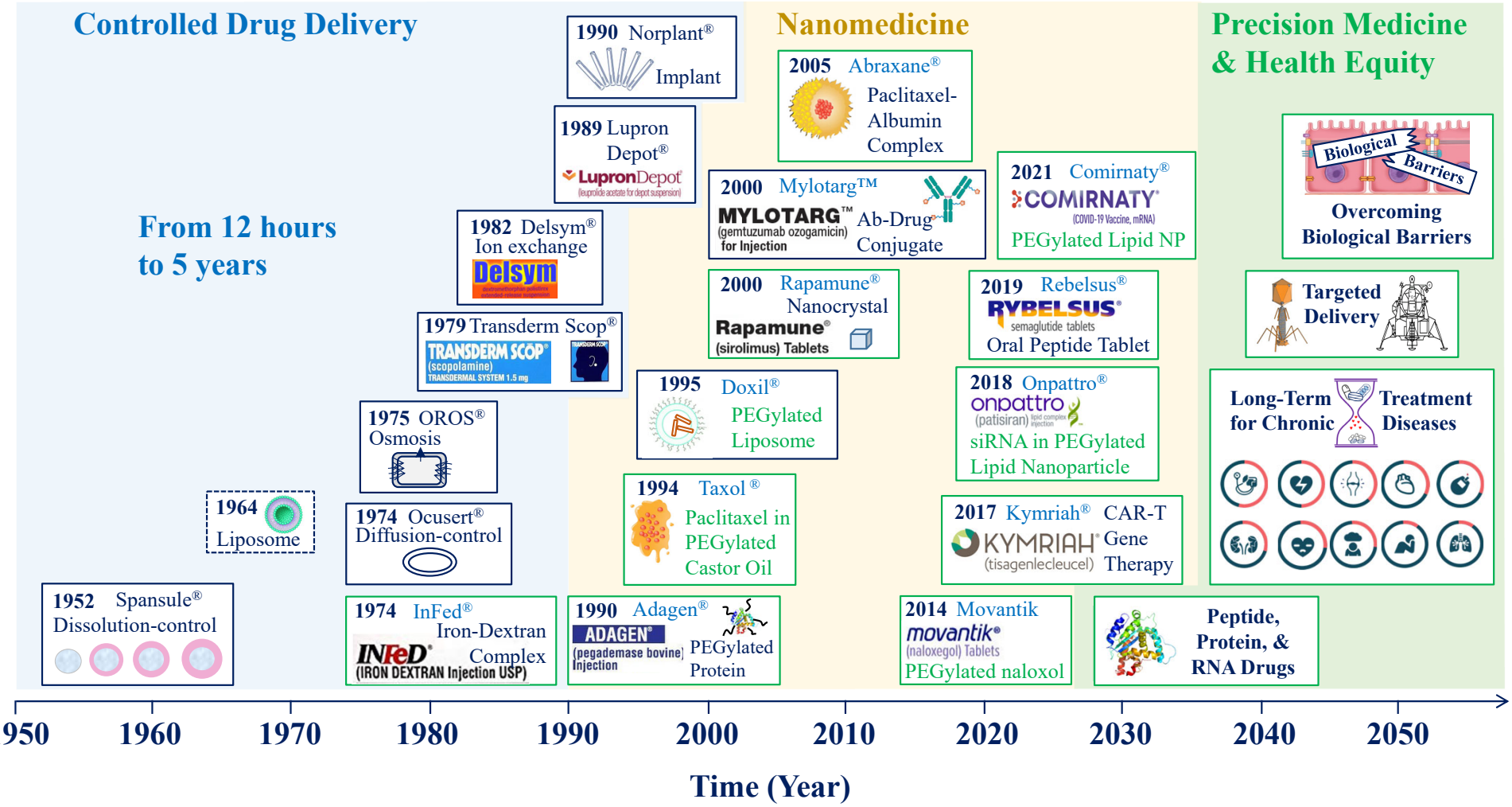
2018 Onpattro®
onpattro (patisiran) lipid complex injection
RNAi in PEGylated Lipid Nanoparticle

2017 Kymriah® CAR-T Gene Therapy
KYMRIAH® (tisagenlecleucel)

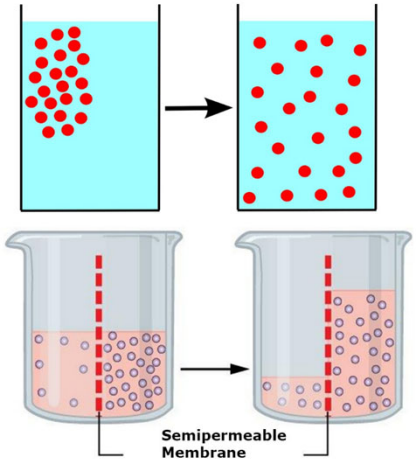
2021 Comirnaty® PEGylated Lipid Nanoparticle
COMIRNATY® (COVID-19 Vaccine, mRNA)

Controlled Drug Delivery Mechanisms

Evolution of Controlled Drug Delivery Systems



Diffusion



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.

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

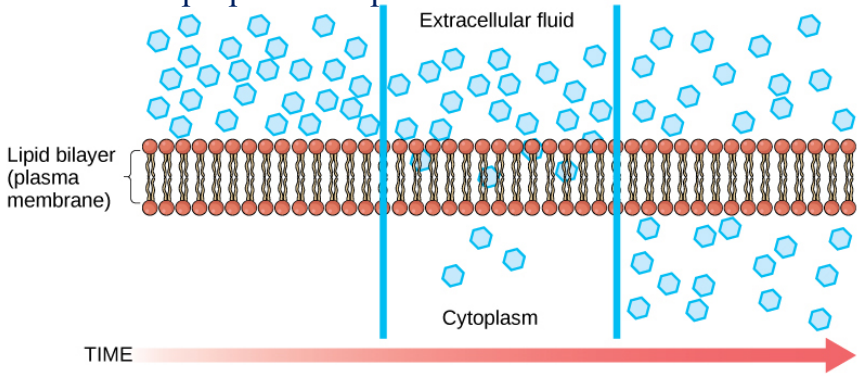
$$D = \frac{kT}{6\pi\eta r}$$

$$x = \sqrt{2Dt}\ cm^2/s$$

(One dimensional diffusion)

Permeation

Movement through a membrane depends on the properties of permeant and membrane.

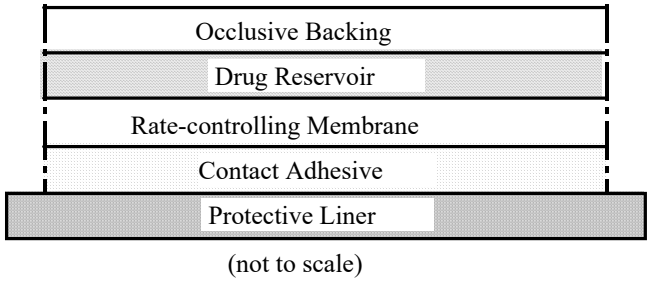


https://openoregon.pressbooks.pub/mhccbiology101/chapter/diffusion/

Controlled Release Dosage Forms: Major Components

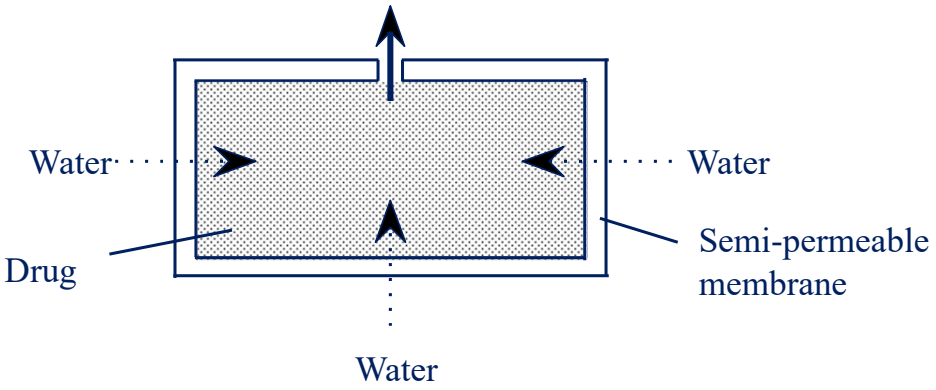
Drug	+	Drug Delivery Module	+	Platform
		Reservoir		
		Delivery Portal (Exit)		
		Energy Source		
		Rate Controller		

Transdermal Patch



(not to scale)

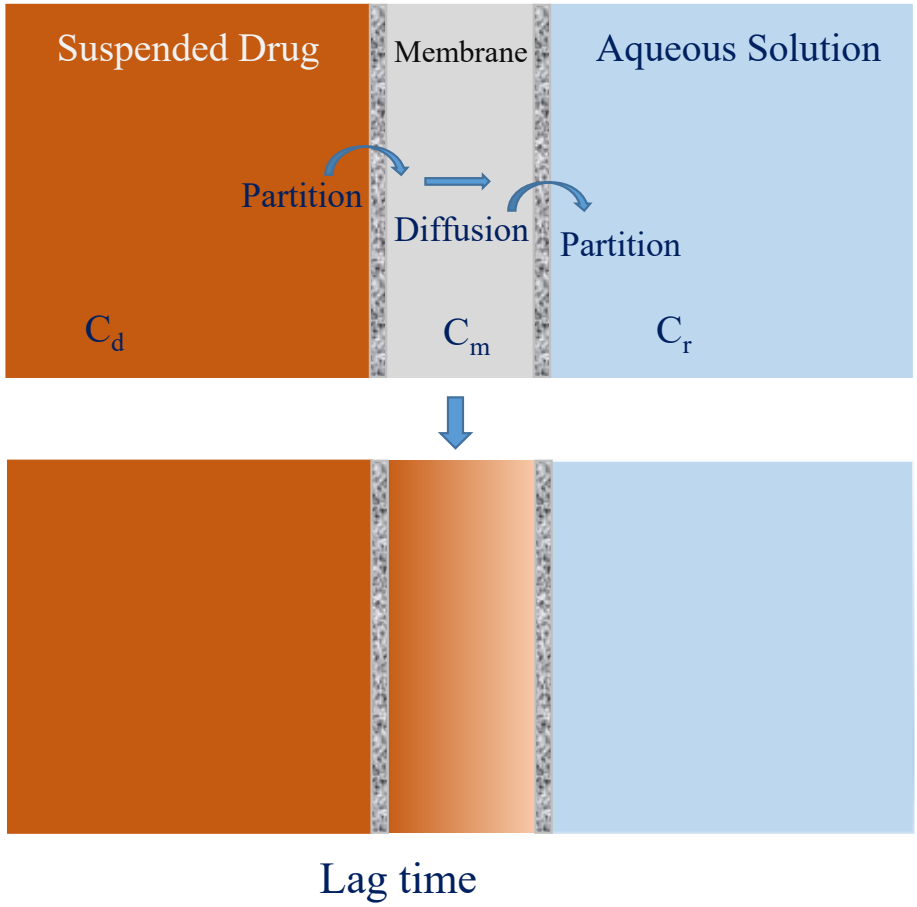
Osmotic Tablet



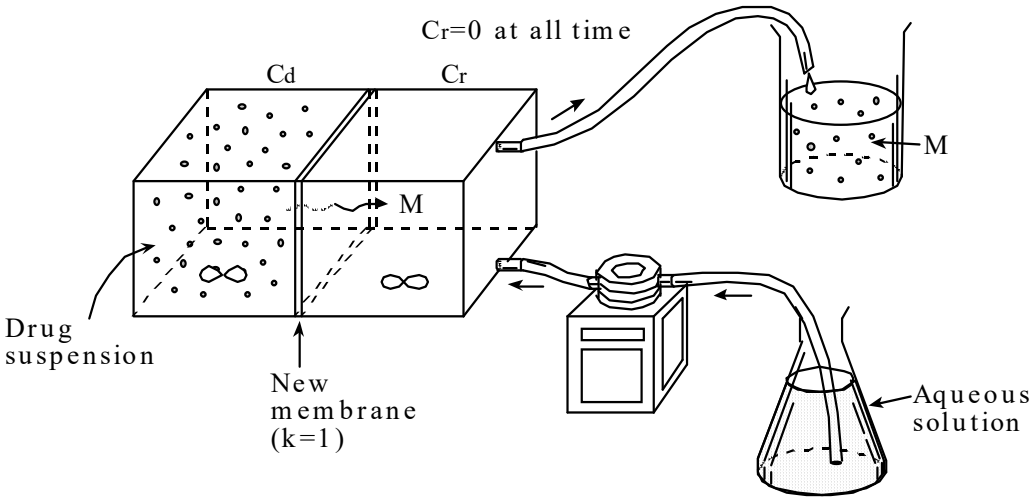
Drug Release through a Polymer Membrane (Solution-Diffusion Membrane)

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.



Lag time



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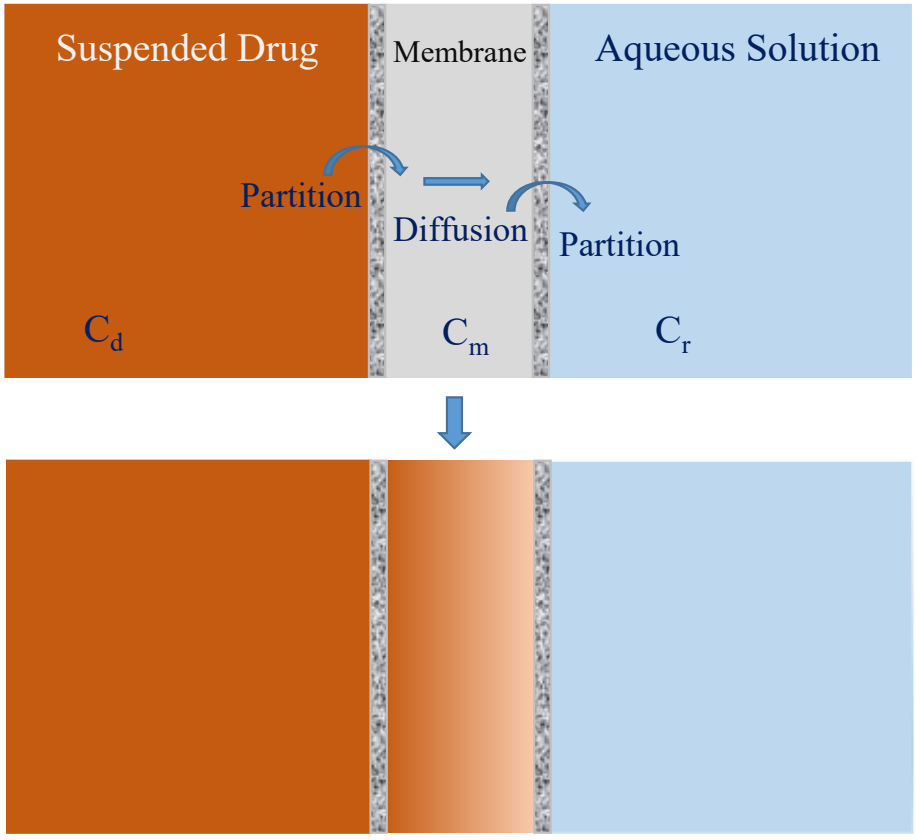

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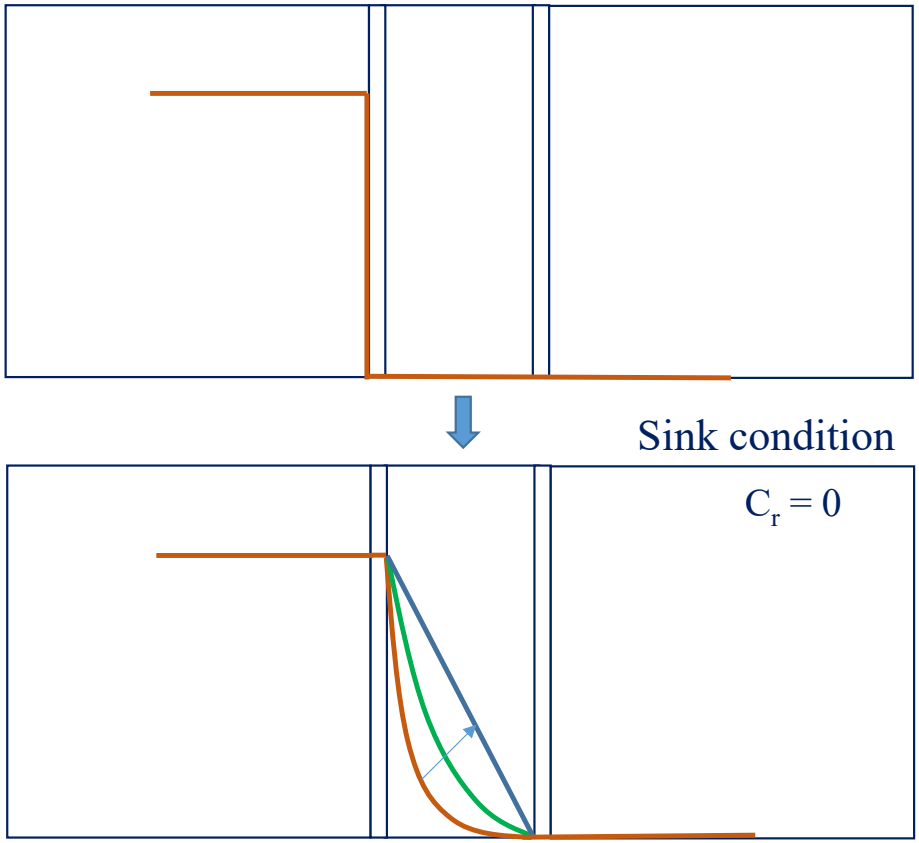
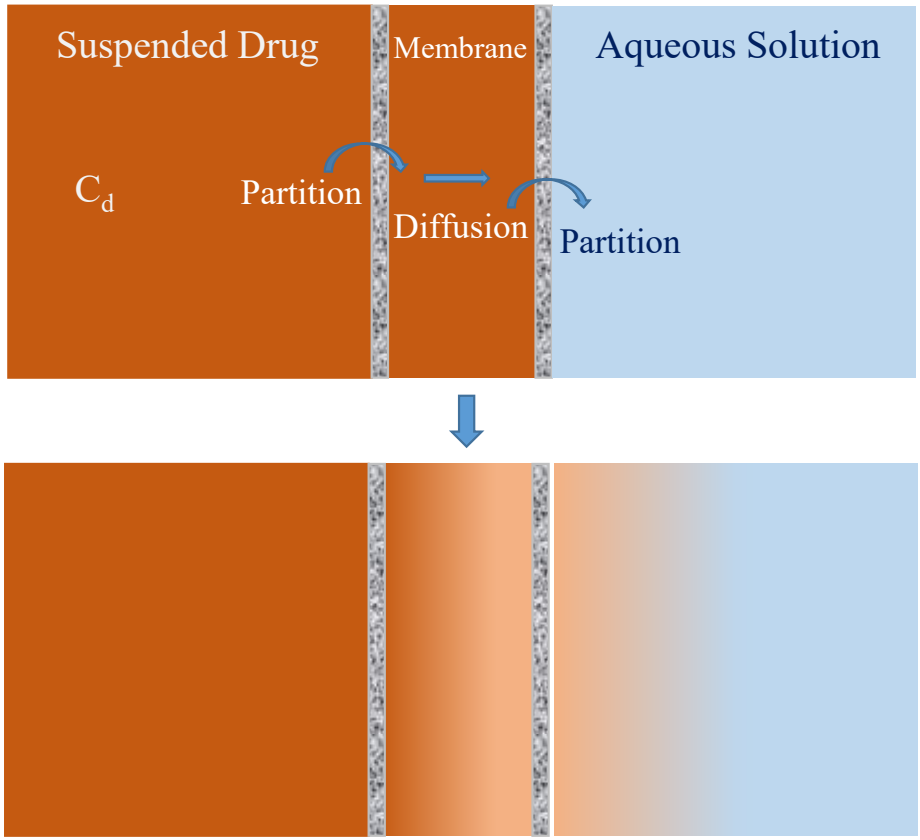


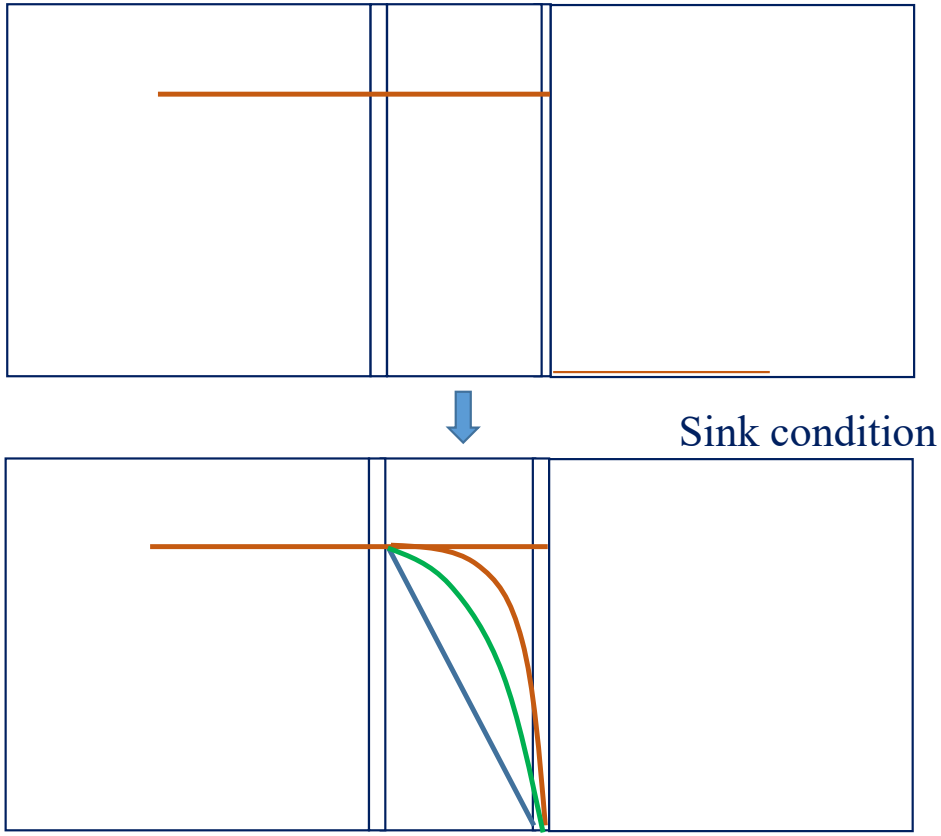
Lag time

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

A nonporous, homogeneous polymer membrane presaturated with a drug

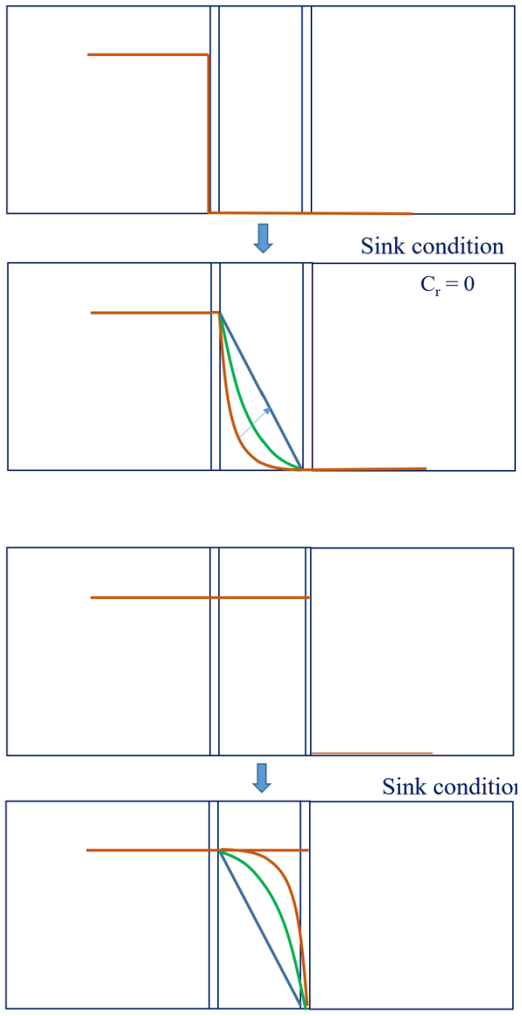


Burst effect



Lag time

Different Solubilities in Water and in Polymer



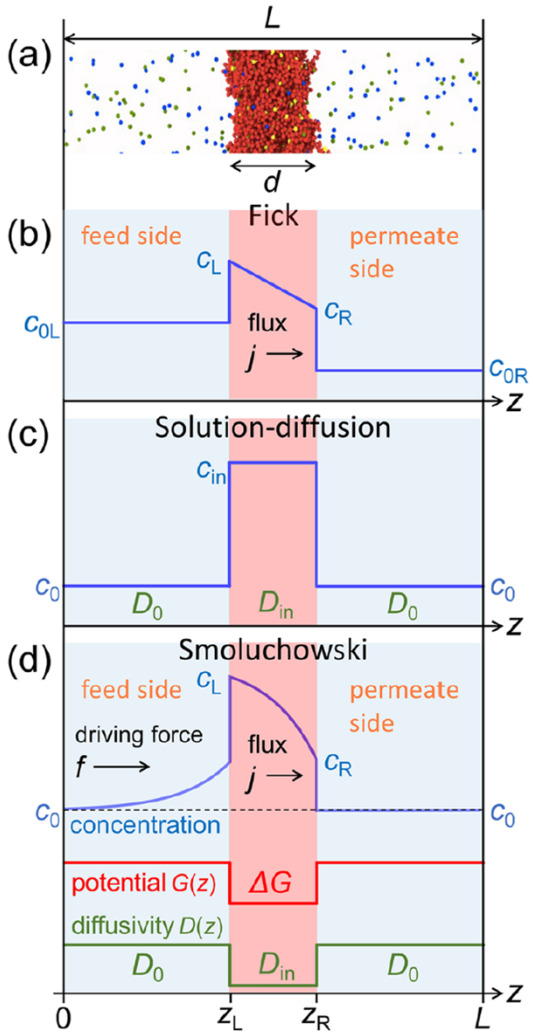
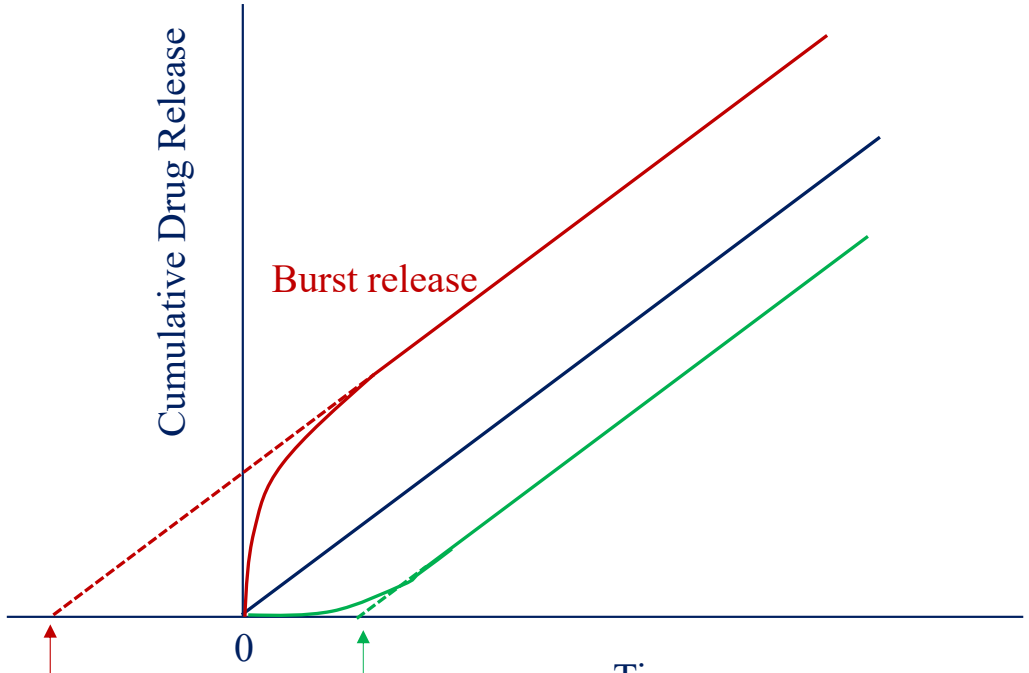


Figure 1. (a) Polymer network membrane (red) of thickness d, located at the center of a system of length L with penetrants (small blue and green spheres). (b–d) Various scenarios of membrane permeation in a continuum representation. (b) Fick's type of permeation: The penetrant flux j is generated by different bulk reservoir concentrations of penetrants c_{0L} (feed side) and c_{0R} (permeate side). (c) Solution–diffusion model with equilibrium penetrant concentrations c_0 in bulk and c_{in} inside the membrane and corresponding diffusion coefficients D_0 and D_{in}. (d) Smoluchowski-type permeation in nonequilibrium: The penetrant flux j is generated by a driving force f (any forces apart from the Fick type) acting on penetrants, which flows from the feed side to the permeate side. $G(z)$ and $D(z)$ are the position-dependent membrane potential and diffusivity, respectively (see eqs 15 and 16).

Kim 2022, Permeability of polymer membranes beyond linear response

Lag Time Release vs Burst Release

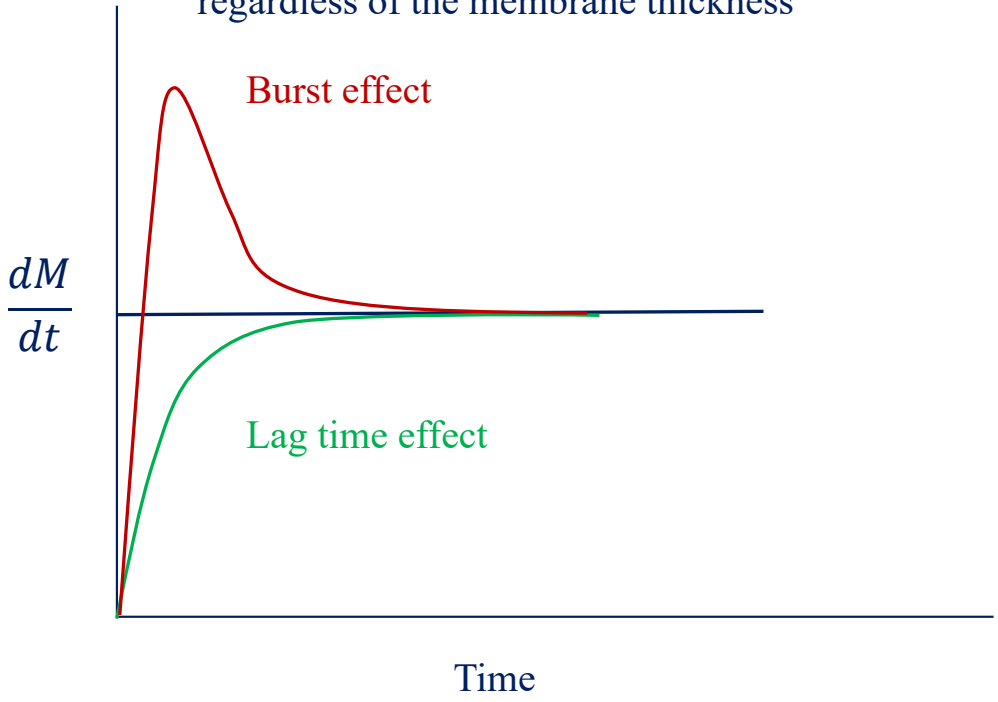
Slope = Steady-state release rate



$t_B = \frac{h^2}{3D}$

$t_L = \frac{h^2}{6D}$ (Lag time)

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



$$M = S \cdot D \cdot K \frac{\Delta C}{h}\left(t + \frac{h^2}{3D}\right)$$

$$M = S \cdot D \cdot K \frac{\Delta C}{h}\left(t - \frac{h^2}{6D}\right)$$

Mechanisms of Controlled Drug Release

Physical Mechanisms

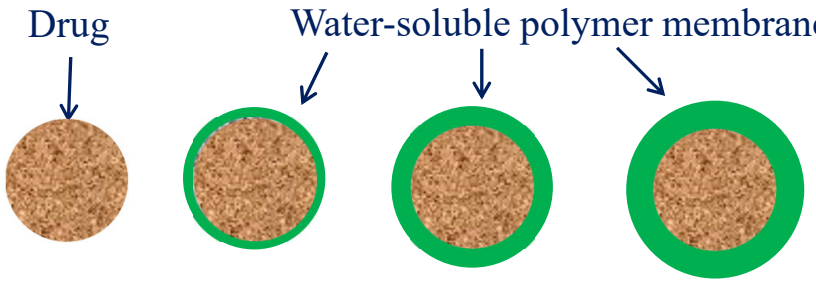
1. Dissolution
   - Reservoir System
   - Matrix System
2. Diffusion
   - Reservoir System (Reservoir = Encapsulated)
   - Monolithic System
     - Monolithic Solution System (Monolithic = Matrix)
     - Monolithic Dispersion System
3. Osmosis
4. Ion-Exchange

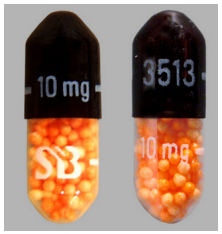
Chemical Mechanisms

5. Chemical Degradation
6. Enzymatic Degradation

Dissolution-Controlled System

Reservoir System (= Encapsulated Dissolution System)

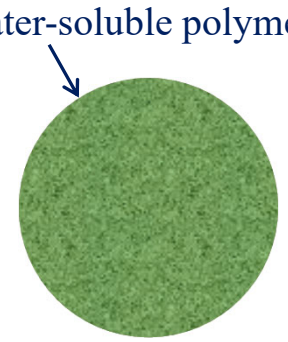




Spansule

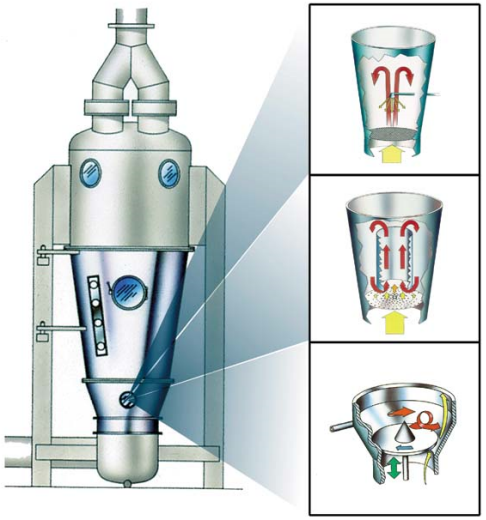
Dissolution of the polymeric material (e.g., PEG) is the key to this mechanism. All of the polymers used must be water soluble or degradable.

Matrix Dissolution System



The drug is homogeneously distributed throughout the polymer matrix.

As the polymer matrix dissolves, drug molecules are released.

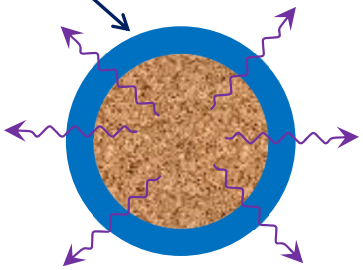


Fluid-Bed Wurster Coater

Diffusion-Controlled System

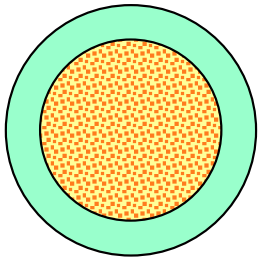
Reservoir System (= Encapsulated Diffusion System)

Water-insoluble polymer membrane

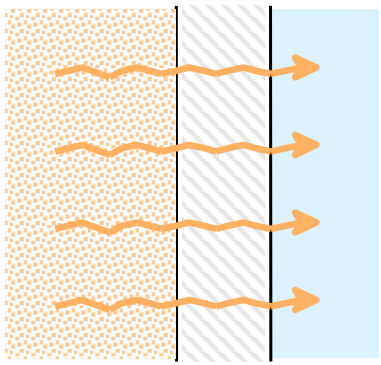


Dissolution of the polymeric material is the key to this mechanism. All of the polymers used must be water soluble or degradable.

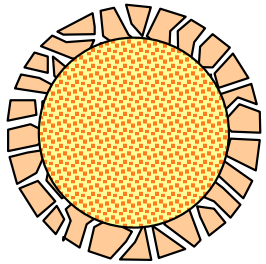
Nonporous membrane



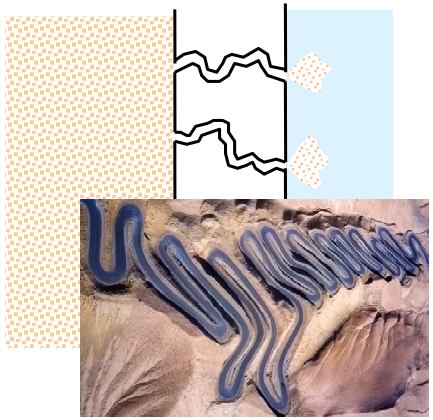
Drug must diffuse through solution-diffusion membrane



Microporous membrane

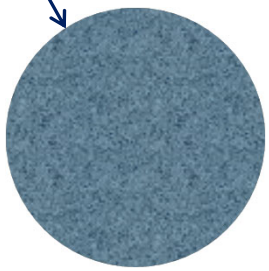


Drug is released through micropores (usually filled with water or oil)



Monolithic Diffusion System

Water-insoluble polymer matrix

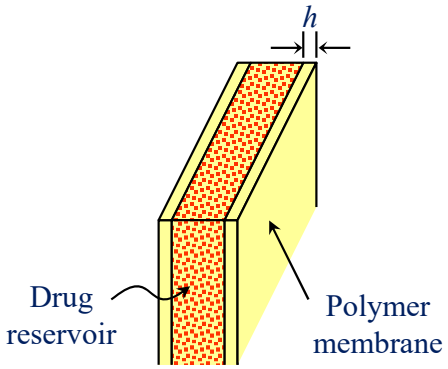


The drug is homogeneously distributed throughout the polymer matrix.

As the polymer matrix dissolves, drug molecules are released.

Diffusion-Controlled System

1-Dimension Reservoir Device (Slab)

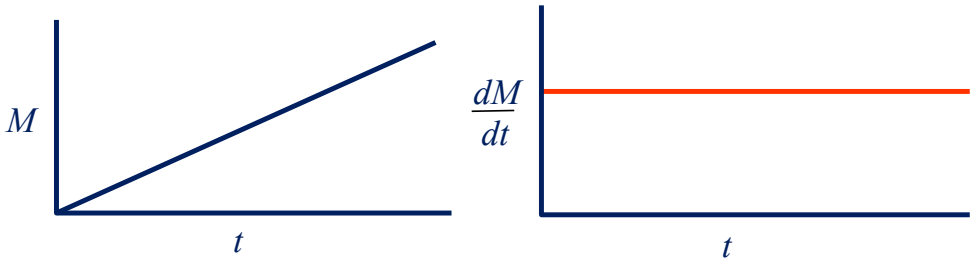


$$M = \frac{S \cdot D \cdot K \cdot \Delta C \cdot t}{h}$$

$$\frac{dM}{dt} = \frac{S \cdot D \cdot K \cdot \Delta C}{h}$$

$$\Delta C = C_s - C$$

K = partition coefficient



Drug release is zero order.

Norplant® Subdermal Implant

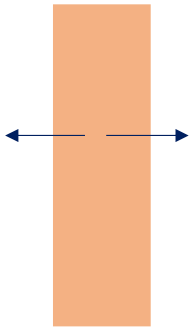
Six matchstick-size silicon rubber rods inserted into the upper arm. Each rod contains 36 mg levonogestrel.
The system releases 85 mg/d initially, which declines to 30 mg/d during its useful life (up to 7 years).

Microporous polypropylene film (Celgard®) in disposable butane lighters

Maintain constant flow and flame height, regardless of ambient pressure and fuel level.

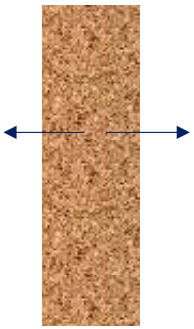
Diffusion-Controlled Monolithic System

Monolithic Solution System



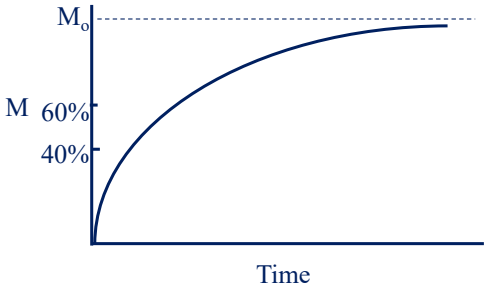
C_{max} is the drug solubility in solution.

Monolithic Dispersion System



C_{max} depends on the solid drug content.

C_{max}: The maximum drug concentration



Decrease in release rate due to increase in diffusion path length

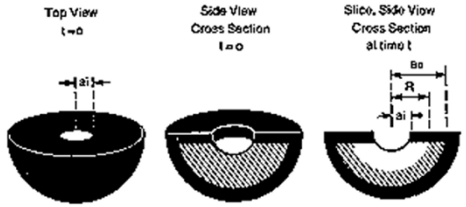


FIGURE 5. Diagram of an inwardly-releasing hemisphere; a, is the inner radius, a, is the outer radius, and R is the distance to the interface between the dissolved region (white area) and the dispersed zone (diagonal lines). Black represents laminated regions through which release cannot occur. (From Hsieh, D. S. T. et al., *J. Pharm. Sci.*, 72, 17, 1983. With permission.)

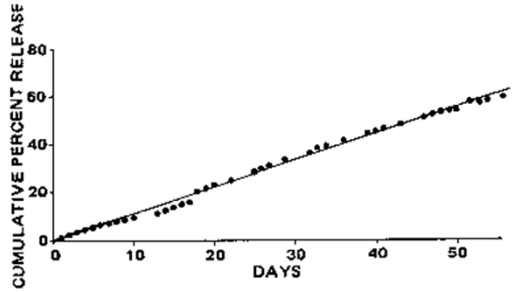


FIGURE 6. Cumulative release of bovine serum albumin vs. time. The matrix was made of ethylene-vinyl acetate copolymer and bovine serum albumin. Standard error of the mean of the cumulative release at each time point was within 12%. (From Hsieh, D. S. T. et al., *J. Pharm. Sci.*, 72, 17, 1983. With permission.)

Japanese Beetle Lure & Trap

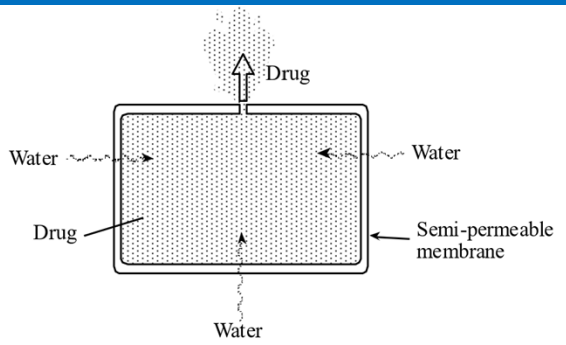
- Lures beetles with pheromones
- No sprays required
- Replace lures every 4-6 weeks

Attracts adult using an irresistible pheromone and floral lure. Set out in mid-June, 50 ft. upwind of vulnerable plants. Includes trap assembly, large-capacity bag and lures. Japanese Beetle Trap lures should be replaced every four to six weeks.

Japanese beetles are metallic green and copper-colored, and usually grow to about 1/2" long. They will eat almost any plant, but especially love beans and corn. This beetle's larvae are rarely noticed, but their diet of grass and vegetable roots can reduce crop yields and weaken lawns.

https://www.gurneys.com/product/japanese-beetle-trap

Osmosis-Controlled System



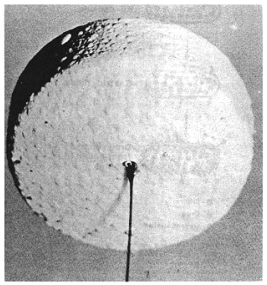
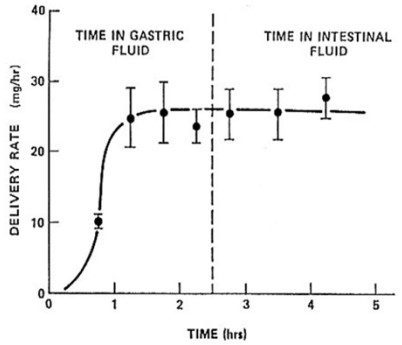
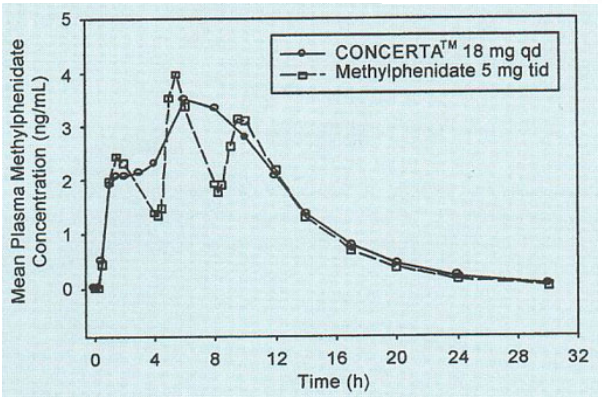


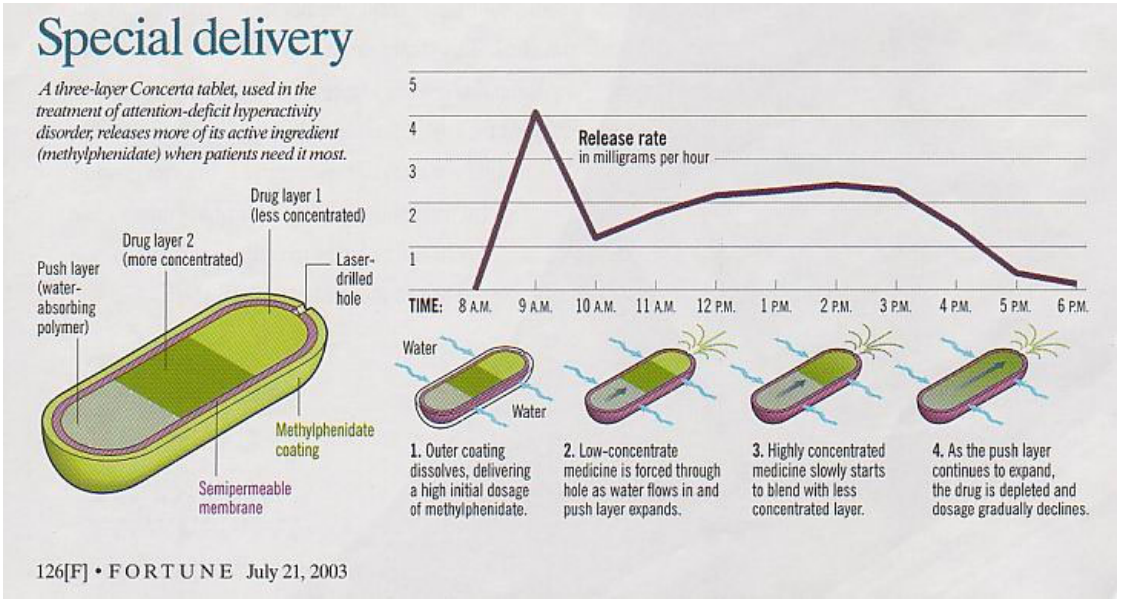
FIGURE 13. Demonstration model of an Oros® tablet (courtesy of Merck Sharp & Dohme, The Netherlands).

Typical in vitro release rate of an OROS® tablet

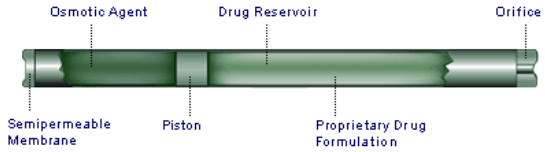


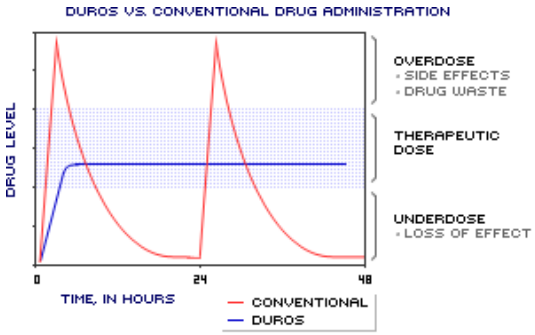


Mean plasma methylphenidate concentrations with Concerta and Immediate-release tablet.



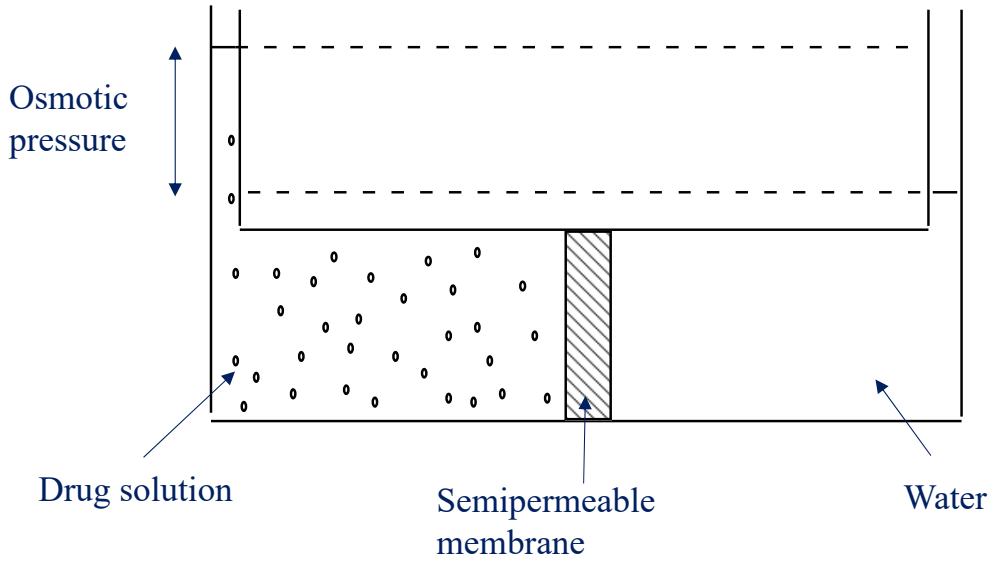
DUROS® implant technology DURECT



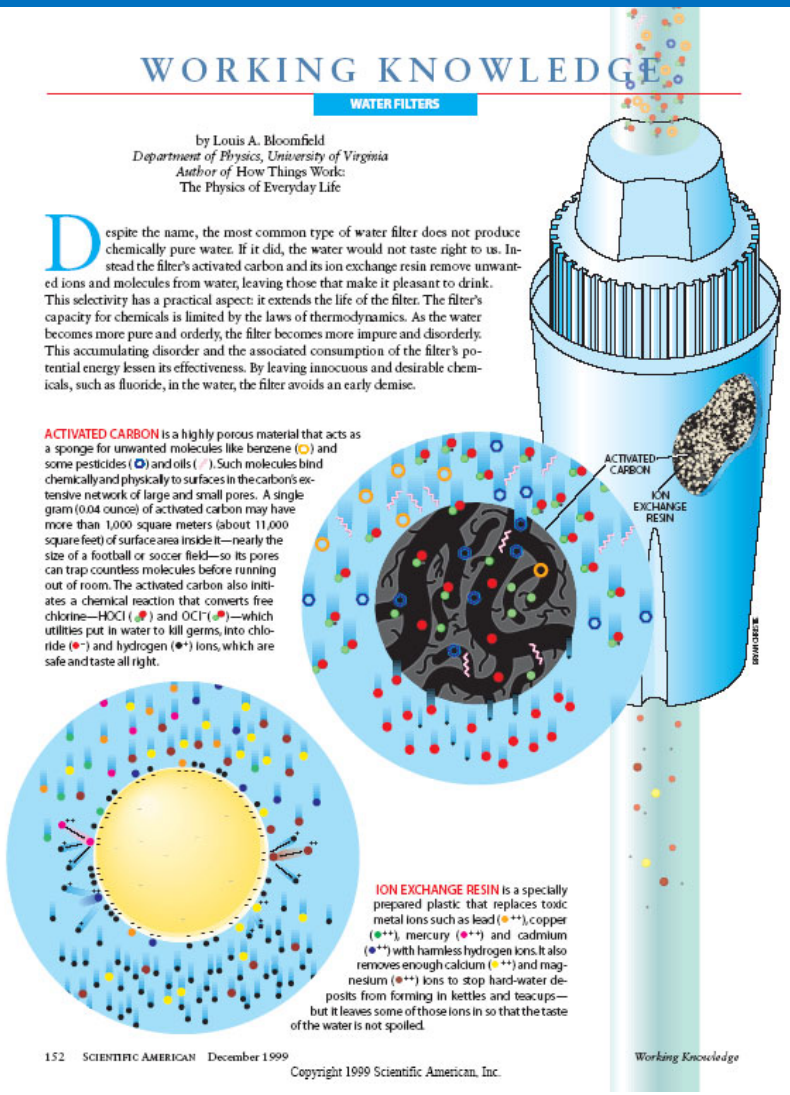


Reverse Osmosis

Seawater undergoes reverse osmosis, in which high pressure forces the water through membranes that remove impurities.



Ion Exchange-controlled Drug Release



WORKING KNOWLEDGE

WATER FILTERS

by Louis A. Bloomfield
Department of Physics, University of Virginia
Author of How Things Work:
The Physics of Everyday Life

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 its ion exchange resin remove unwanted ions and molecules from water, leaving those that make it pleasant to drink. This selectivity has a practical aspect: it extends 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 orderly, the filter becomes more impure and disorderly. This accumulating disorder and the associated consumption of the filter's potential energy lessen its effectiveness. By leaving innocuous and desirable chemicals, such as fluoride, in the water, the filter avoids an early demise.

ACTIVATED CARBON is a highly porous material that acts as a sponge for unwanted molecules like benzene (○) and some pesticides (●) and oils (/). Such molecules bind chemically and physically to surfaces in the carbon's extensive network of large and small pores. A single gram (0.04 ounce) of activated carbon may have more than 1,000 square meters (about 11,000 square feet) of surface area inside it—nearly the size of a football or soccer field—so its pores can trap countless molecules before running out of room. The activated carbon also initiates a chemical reaction that converts free chlorine—HOCl (●●) and OCl^- (●●)—which utilities put in water to kill germs, into chloride ($\bullet^-$) and hydrogen ($\bullet^+$) ions, which are safe and taste all right.

ACTIVATED CARBON

ION EXCHANGE RESIN

ION EXCHANGE RESIN is a specially prepared plastic that replaces toxic metal ions such as lead ($\bullet^{++}$), copper ($\bullet^{++}$), mercury ($\bullet^{++}$) and cadmium ($\bullet^{++}$) with harmless hydrogen ions. It also removes enough calcium ($\bullet^{++}$) and magnesium ($\bullet^{++}$) ions to stop hard-water deposits from forming in kettles and teacups—but it leaves some of those ions in so that the taste of the water is not spoiled.

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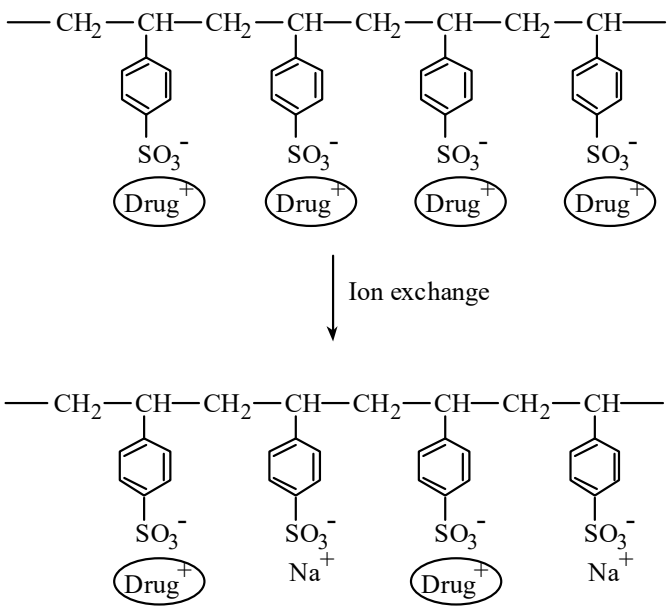
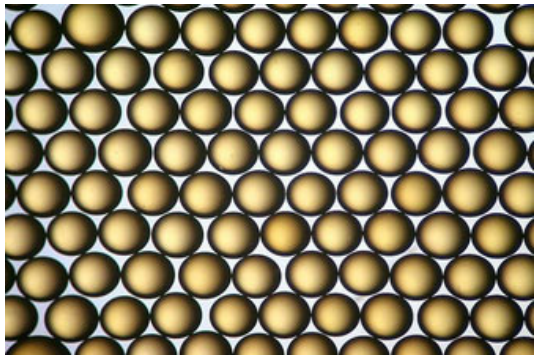
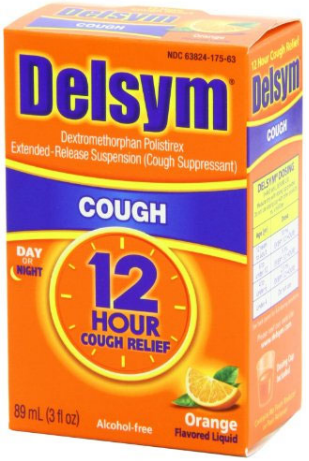
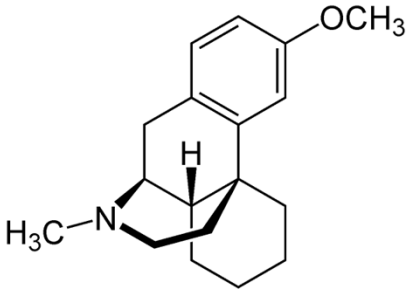
Working Knowledge









Dextromethorphan

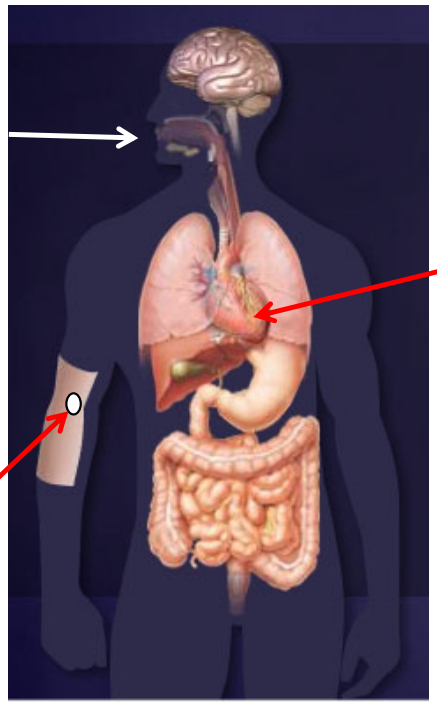
Evolution of Drug Delivery Systems

Drug Delivery Routes

Oral Delivery:
<1 min ~ > 1 day

Transdermal:
1 day ~ 1 week

I.V. Infusion
~ 1 day

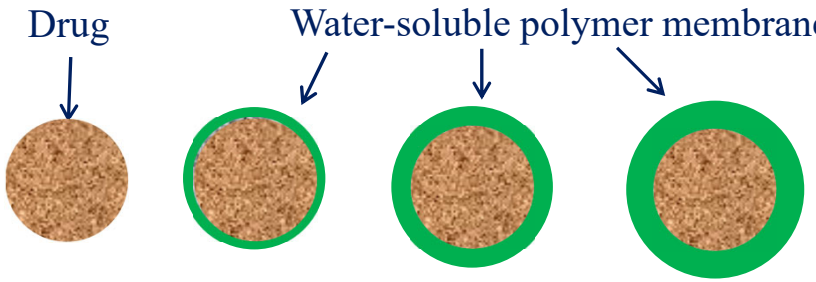


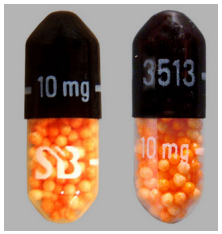
Localized Delivery:
1 month ~ 1 year

Implants (IM, SQ):
1 month ~ 1 year

Dissolution-Controlled System

Reservoir System (= Encapsulated Dissolution System)





Spansule

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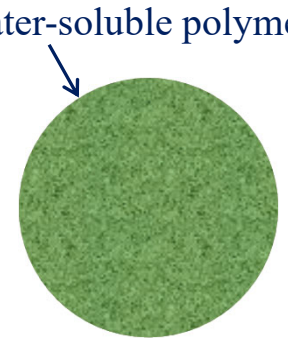
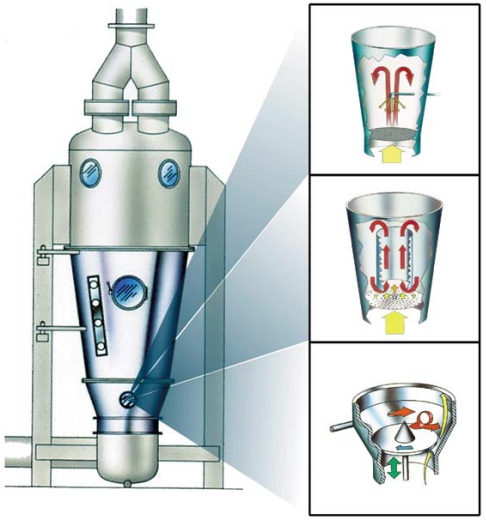
Matrix Dissolution System



The drug is homogeneously distributed throughout the polymer matrix.

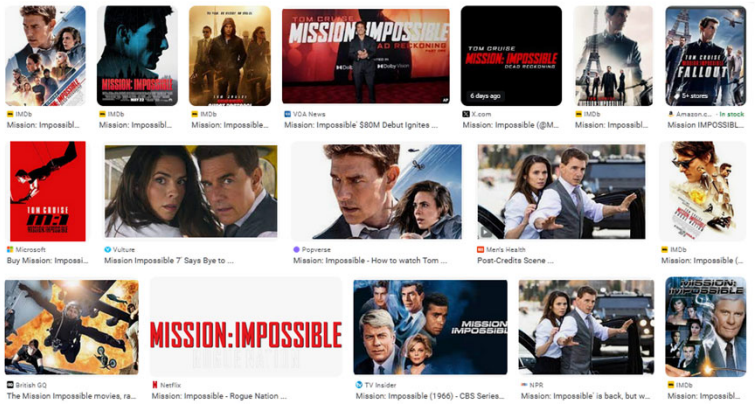
As the polymer matrix dissolves, drug molecules are released.



Fluid-Bed Wurster Coater

Columbo: Uneasy Lies the Crown (1990)

Mission: Impossible (1966)

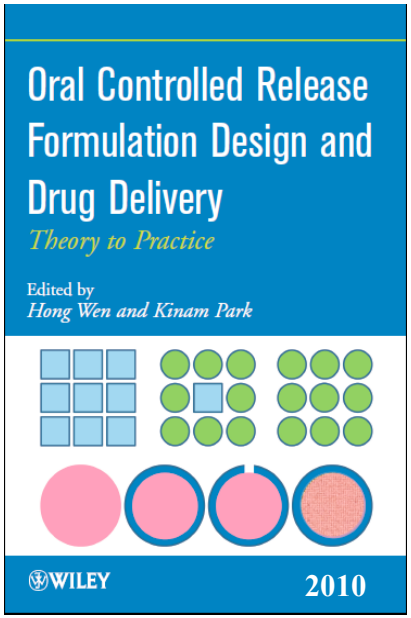


Good morning, Mr. Phelps. ---. Your mission, Jim, should you choose to accept it, is to ---. As always, should you or any of member of your team be caught or killed, the Secretary will disavow any knowledge of your actions. This tape will self-destruct in five seconds. Good luck to you, Jim.

Oral Controlled Drug Delivery Systems

Highly Successful Oral Sustained Release Formulations

12-hour delivery, 24-hour delivery



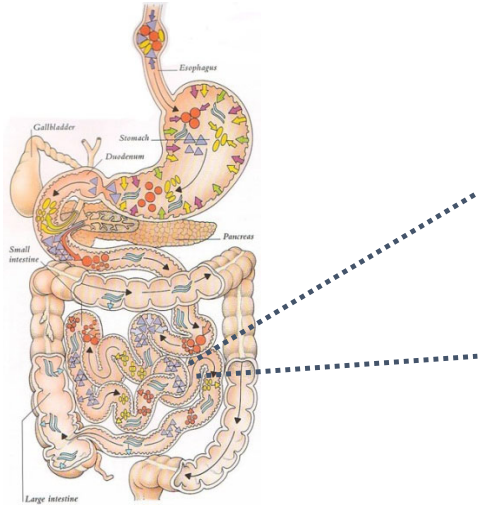
Ahmed & Naini: Generic oral controlled release product development: Formulation and process considerations. Ch. 19.

Sklar SH. Extended-release drug patents: can they save big pharma's blockbuster medicines from the generic scrap heap?. *Pharm. Law Ind. Rep.* 2006;4(6):1–8.

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

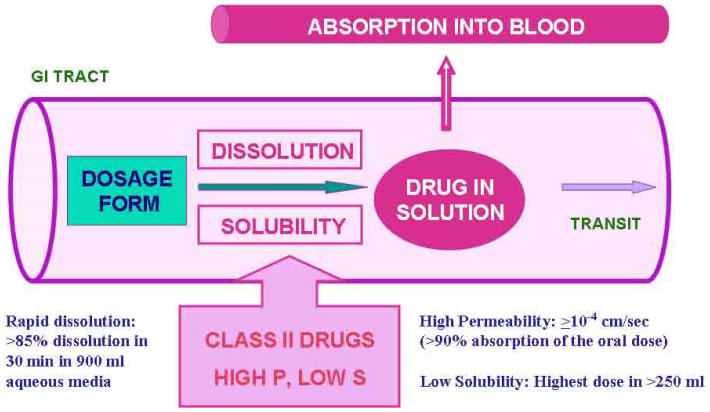
Brand Product	Generic Name	Patent(s)	Claim Types
Adderall XR®	Amphetamine salts	US 6,322,819	FPK
		US 6,605300	FPK
Biaxin® XL	Clarithromycin	US 6,010,718	FPK
		US 6,551,616	F
		US 6,872,407	PK
Concerta®	Methylphenidate	US 6,919,373	PK
		US 6,930,129	PK
Depakote® ER	Divalproex	US 6,419,953	F
		US 6,511,678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

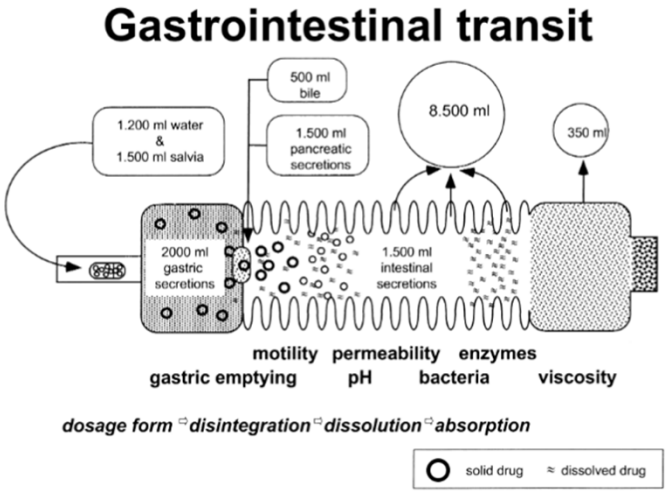
Need for Formulations of Poorly-Soluble Drugs



Increased absorption of poorly water-soluble drugs

Drug absorption from the GI tract





Lobenberg 2000, Modern bioavailability, bioequivalence and biopharmaceutics classification system

Biopharmaceutics Classification System

Table I
BCS classification of drugs and in vitro/in vivo correlation expectations for immediate release products based on the biopharmaceutics class[a]

Class	Solubility	Permeability	IVIVC expectation
I	High	High	IVIVC if the dissolution rate is slower than the gastric emptying rate, otherwise limited or no correlation
	(5~10%) →35%		
II	Low	High	IVIVC expected if the in vitro dissolution rate is similar to the in vivo dissolution rate, unless the dose is very high
	(60~70%)→30%		
III	High	Low	Absorption (permeability) is rate determining and limited or no IVIVC with dissolution rate
	(5~10%) →25%		
IV	Low	Low	Limited or no IVIVC expected
	(10~20%) →10%		

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 biowaiver 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.

(G.L. Amidon, H. Lennernas, V.P. Shah, J.R. Crison, A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, Pharm. Res. 12 (1995) 413-420).

Poorly Soluble Drugs: Amorphous Solid Dispersion

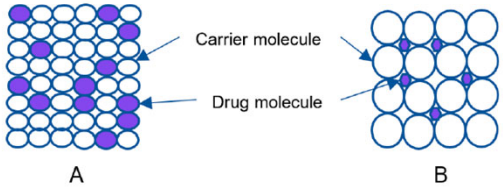


Figure 4. Schematic structure of the solid solution.

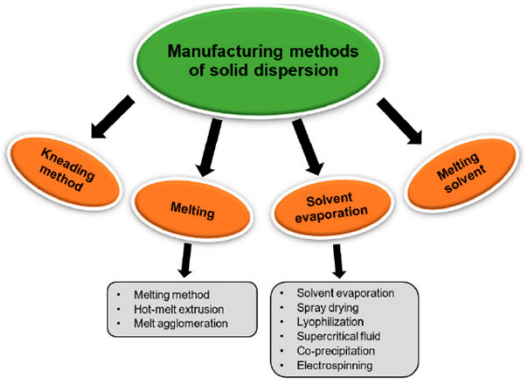


Figure 5. Manufacturing methods of solid dispersion.

Methods	Drugs
Melting/fusion method	Sulfathiazole [39], clotrimazole [43], albendazole [54], tacrolimus [61], fenofibrate [75], furosemide [85], paclitaxel [86], manidipine [88], olanzapine [89], diacerein [90]
Solvent evaporation method	Dutasteride [23], tadalafil [50], glimepiride [53], nimodipine [59], diclofenac [68], azithromycin [91], tectorigenin [92], flurbiprofen [93], cilostazol [94], ticagrelor [95], piroxicam [96], indomethacin [97], loratadine [98], abietic acid [99], efavirenz [100], repagnilide [101], prednisolone [102]
Hot-melt extrusion method	Ritonavir [37], naproxen [46], oleanolic acid [103], efavirenz [104], tamoxifen [105], lafutidine [106], disulfiram [107], bicalutamide [108], itraconazole [109], miconazole [110], glyburide [111]
Lyophilization/Freeze-drying	Nifedipine and sulfamethoxazole [112], celecoxib [113], meloxicam [114], docetaxel [115]
Co-precipitation method	Silymarin [116], celecoxib [117], GDC-0810 [118]
Supercritical fluid method	Ketoprofen [66], irbesartan [119], apigenin [120], carbamazepine [121], glibenclamide [122], carvedilol [123]
Spray-drying method	Nilotinib [124], spironolactone [125], valsartan [126], rebamipide [127], artemether [128], naproxen [129]
Kneading method	Cefixime [67], efavirenz [100], domperidone [130]

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

Table 2. List of commercial solid dispersions.

Products	Drugs	Polymers	Company
Afeditab®	Nifedipine	Poloxamer or PVP	Elan Corp, Ireland
Cesamet®	Nabilone	PVP	Lilly, USA
Cesamet®	Nabilone	PVP	Valeant Pharmaceuticals, Canada
Certican®	Everolimus	HPMC	Novartis, Switzweland
Gris-PEG®	Griseofulvin	PEG	Novartis, Switzweland
Gris-PEG®	Griseofulvin	PVP	VIP Pharma, Denmark
Fenoglide®	Fenofibrate	PEG	LifeCycle Pharma, Denmark
Nivadil®	Nivaldipine	HPC/HPMC	Fujisawa Pharmaceuticals Co., Ltd
Nimotop®	Nimodipine	PEG	Bayer
Torcetrapib®	Torcetrapib	HPMC AS	Pfizer, USA
Ibuprofen®	Ibuprofen	Various	Soliqs, Germany
Incivek®	Telaprevir	HPMC AS	Vertex
Sporanox®	Itraconazole	HPMC	Janssen Pharmaceutica, Belgium
Onmel®	Itraconazole	HPMC	Stiefel
Prograf®	Tacrolimus	HPMC	Fujisawa Pharmaceuticals Co., Ltd
Cymbalta®	Duloxetine	HPMC AS	Lilly, USA
Noxafil®	Posaconazole	HPMC AS	Merck
LCP-Tacro®	Tacrolimus	HPMC	LifeCycle Pharma, Denmark
Intelence®	Etravirine	HPMC	Tibotec, Yardley, PA
Incivo®	Etravirine	HPMC	Janssen Pharmaceutica, Belgium
Rezulin®	Troglitazone	PVP	Pfizer, USA
Isoptin SRE-240®	Verapamil	Various	Soliqs, Germany
Isoptin SR-E®	Verapamil	HPC/HPMC	Abbott Laboratories, USA
Crestor®	Rosuvastatin	HPMC	AstraZeneca
Zelboraf®	Vemurafenib	HPMC AS	Roche
Zortress®	Everolimus	HPMC	Novartis, Switzweland
Kalydeco®	Ivacaflor	HPMC AS	Vertex
Kaletra®	Lopinavir and Ritonavir	PVP/polyvinyl acetate	Abbott Laboratories, USA

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 3. Anticancer drugs investigated for solid dispersions.

Anticancer Drugs	Carriers	Methods	Attributes of Modified Anticancer Drugs	Reference	Years
Bicalutamide	PVP K30	Solvent evaporation	Using PVP K30 as carrier, SD showed the highest cumulative released percentage (about 98% during the initial 10 min) and stability after 6 months	[134]	2006
Docetaxel	HPMC, PEG	Solvent evaporation	The solubility and dissolution of emulsified SD of docetaxel at 2 h were 34.2- and 12.7-fold higher, respectively, compared to the pure conventional drug	[76]	2011
Docetaxel	Poloxamer F68/P85	Freeze-drying	A combination of poloxamer F68 and P85 in the preparation of docetaxel SD not only enhanced solubility, but also improved intestinal permeation	[135]	2016
Etoposide	PEG	Fusion method	The solubility and dissolution of etoposide in SD were higher in comparison with etoposide alone	[136]	1993
Everolimus	HPMC	Co-precipitation	At a ratio of drug to HPMC (1:15), drug release from SD was 75% after 30 min, thereby improving oral absorption of everolimus	[137]	2014
Exemestane	Lipoid® E80S/sodium deoxycholate	Freeze-drying	The exemestane SD showed 4-6-fold increase in absorptive transport compared to the pure drug. In addition, $AUC_{0\text{-}72h}$ of exemestane SD was 2.3-fold higher in comparison with that of drug alone	[138]	2017
Flutamide	PVP K30, PEG, Pluronic F127	Lyophilization	The dissolution of flutamide was higher (81.64%) than the drug alone (13.45%) using poloxamer 407 as a carrier	[77]	2010
Lapatinib	Soluplus, poloxamer 188	Solvent evaporation, hot-melt extrusion	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%)	[78]	2018
Letrozole	CO_2-menthol	Supercritical fluid	Solubility of letrozole SD using supercritical fluid is 7.1 times higher compared to that of the conventional drug	[139]	2018
Megestrol acetate	HPMC, Ryoto sugar ester L1695	Supercritical fluid	The SD with drug: HPMC: Ryoto sugar ester L1695 ratio of 1:2:1 showed over 95% rapid dissolution within 30 min. In addition, AUC and C_{max} (0-24h) of drug in SD were 4.0- and 5.5-fold higher, respectively, compared to those in pure drug	[140]	2015
Oridonin	PVP K17	Supercritical fluid	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	[141]	2011
Paclitaxel	Poloxamer 188, PEG	Fusion method	Paclitaxel SD was successfully prepared, and the drug release from SD was higher than that of the drug alone	[86]	2013
Paclitaxel	HPMC AS	Solvent method	The solubility and permeability of paclitaxel were not increased simultaneously through supersaturation in vivo	[133]	2018
Prednisolone	HP-β-CD, PEG, PVP, PEG 4000, MNT, SMP, Cremophor	Solvent evaporation, melting method, kneading method	The in vitro dissolution of prednisolone SD was improved compared with the pure drug	[87]	2011
Raloxifene	PVP K30	Spray-drying	The absorption of raloxifene from SD showed 2.6-fold enhanced BA in comparison with the conventional drug	[142]	2013
Sorafenib	Soluplus	Spray-drying	The C_{max} and $AUC_{0\text{-}48h}$ of sorafenib in SD formulation increased 1.5- and 1.8-fold, resocetuvely, compared with the pure drug	[143]	2015
Tamoxifen	Soluplus	Hot-melt extrusion	The dissolution and BA of tamoxifen in SD were improved compared with the drug alone	[105]	2018
Vemurafenib	HPMC AS	Solvent-controlled precipitation	The BA of vemurafenib in SD was improved 4~5-fold compared to the conventional drug	[144]	2013

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

Amorphous Solid Dispersions & Crystallinity

Crystallinity: A Complex Critical Quality Attribute of Amorphous Solid Dispersions

Published as part of the Molecular Pharmaceutics virtual special issue "Research Frontiers in Industrial Drug Delivery and Formulation Science".

Dana E. Moseson and Lynne S. Taylor*

Cite This: *Mol. Pharmaceutics* 2023, 20, 4802–4825

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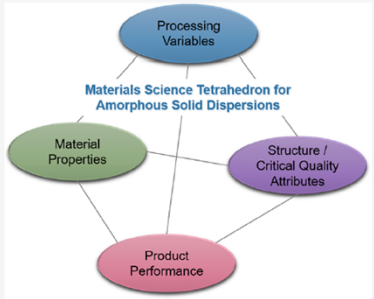
ABSTRACT: Does the performance of an amorphous solid dispersion rely on having 100% amorphous content? What specifications are appropriate for crystalline content within an amorphous solid dispersion (ASD) drug product? In this Perspective, the origin and significance of crystallinity within amorphous solid dispersions will be considered. Crystallinity can be found within an ASD from one of two pathways: (1) incomplete amorphization, or (2) crystal creation (nucleation and crystal growth). While nucleation and crystal growth is the more commonly considered pathway, where crystals originate as a physical stability failure upon accelerated or prolonged storage, manufacturing-based origins of crystallinity are possible as well. Detecting trace levels of crystallinity is a significant analytical challenge, and orthogonal methods should be employed to develop a holistic assessment of sample properties. Probing the impact of crystallinity on release performance which may translate to meaningful clinical significance is inherently challenging, requiring optimization of dissolution test variables to address the complexity of ASD formulations, in terms of drug physicochemical properties (e.g., crystallization tendency), level of crystallinity, crystal reference material selection, and formulation characteristics. The complexity of risk presented by crystallinity to product performance will be illuminated through several case studies, highlighting that a one-size-fits-all approach cannot be used to set specification limits, as the risk of crystallinity can vary widely based on a multitude of factors. Risk assessment considerations surrounding drug physicochemical properties, formulation fundamentals, physical stability, dissolution, and crystal micromeritic properties will be discussed.



KEYWORDS: *amorphous solid dispersion, critical quality attributes, processing, physical stability, dissolution, crystallinity*

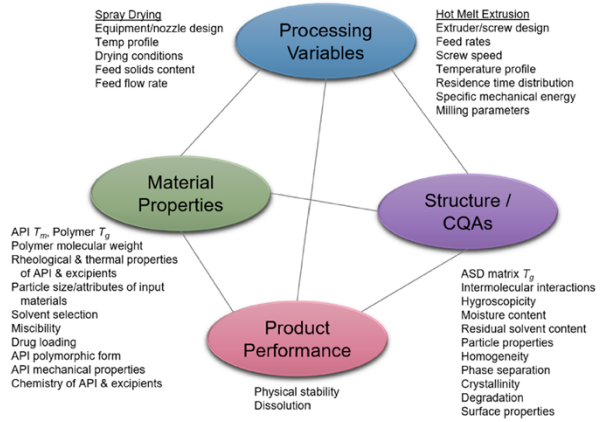


Figure 1. Materials science tetrahedron (MST) as applied to amorphous solid dispersions. The two most popular processing techniques, spray drying and hot melt extrusion, are included to provide examples of key processing variables.

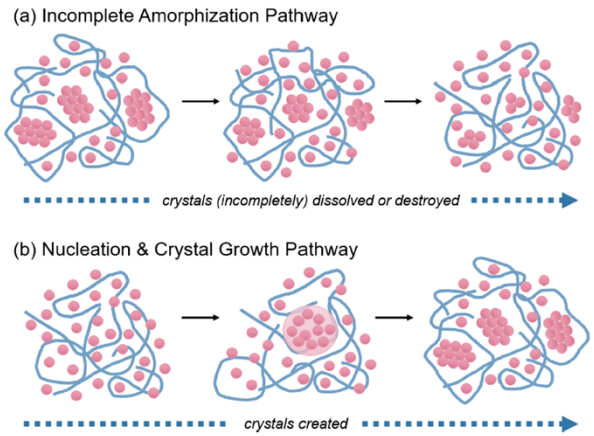


Figure 2. Formation pathways of crystallinity in amorphous solid dispersions: (a) incomplete amorphization, (b) nucleation and crystal growth.

Mesoson 2023, crystallinity- a complex critical quality attribute of amorphous solid dispersions

Oral Delivery of Poorly-Soluble Drugs

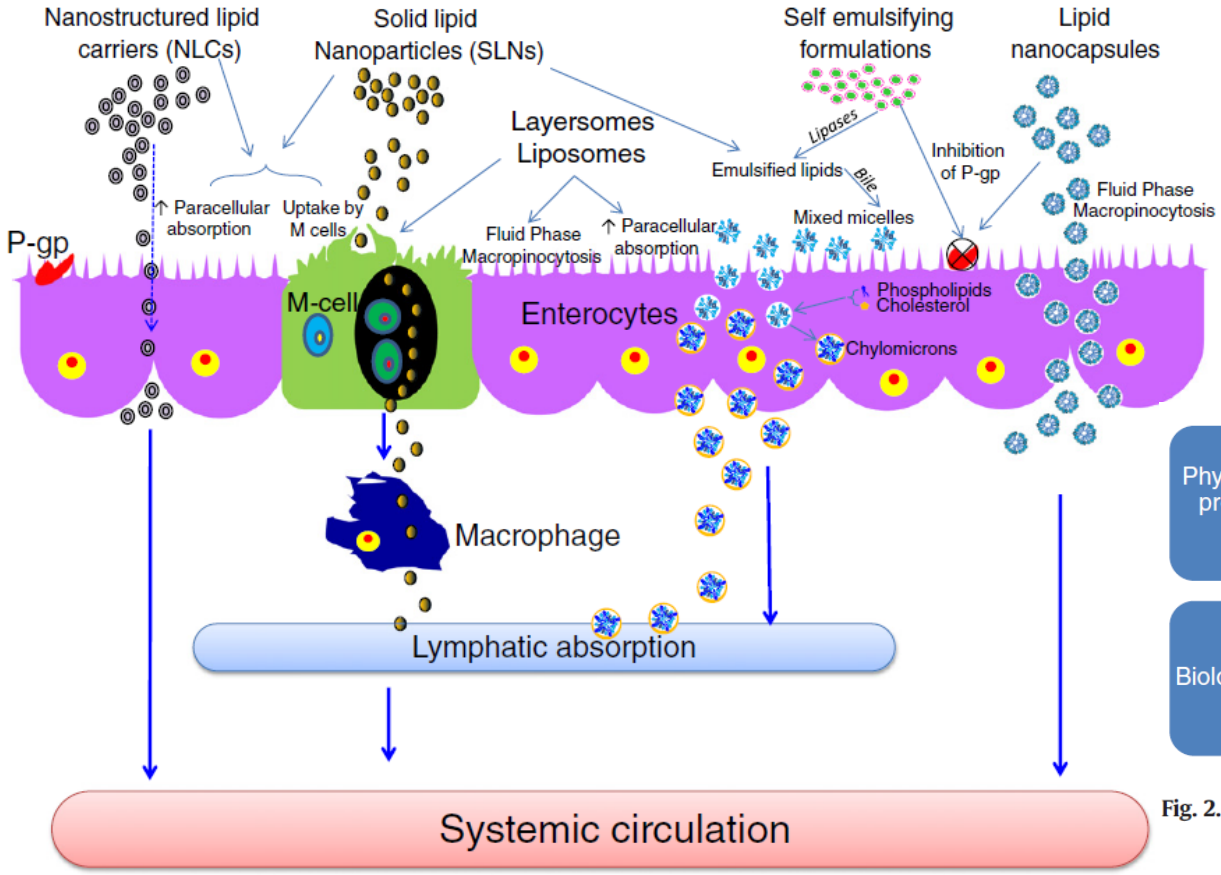


Fig. 11. Absorption mechanisms implemented by lipidic nanocarriers for improving the oral bioavailability of drug substances.

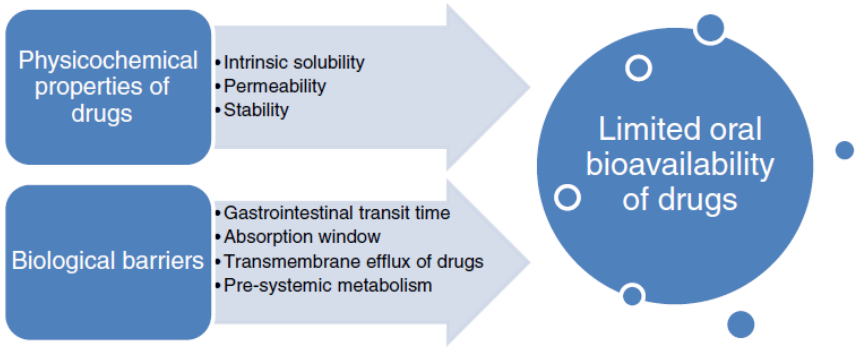


Fig. 2. Schematic representation of the various challenges to the oral delivery of drugs.

Oral delivery of anticancer drugs: Challenges and opportunities.
Kaushik Thanki, Rahul P. Gangwal, Abhay T. Sangamwar, Sanyog Jain. J. Controlled Rel. 170: 15-40, 2013.

Biological Barriers Everywhere

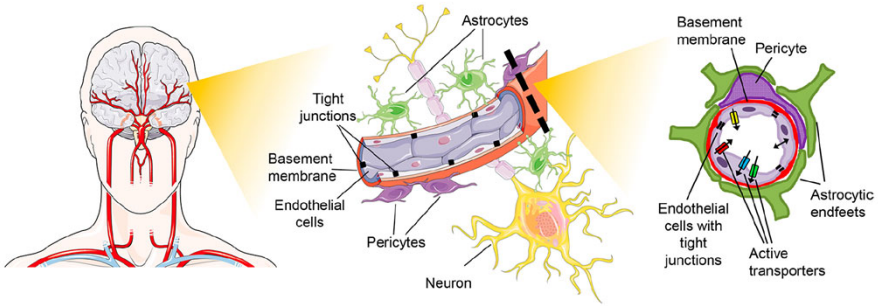


Figure 1. Overview of the multicellular structure of the BBB.

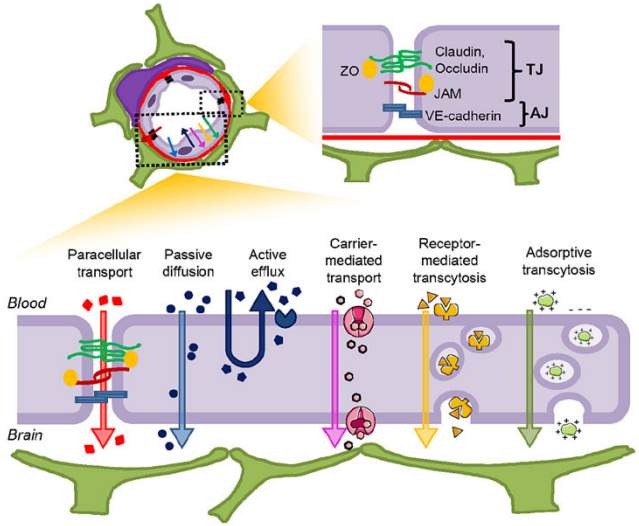


Figure 2. Junctional complexes of the BBB and permeation pathways across it.

Parrasia 2022, Peptides as pharmacological carriers to the brain-promises, shortcomings and challenges

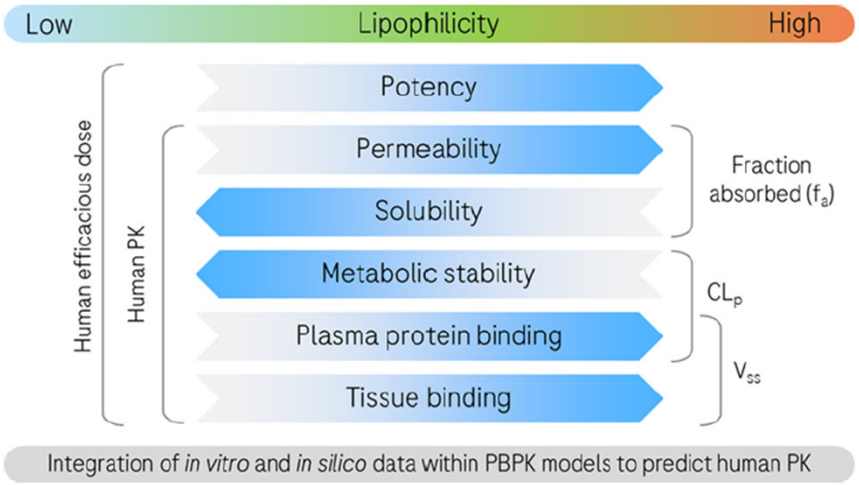


Figure 1. Modulation of lipophilicity causes complex changes in compound PK. Integrative PBPK models can provide a way to predict these effects and estimate an efficacious dose.

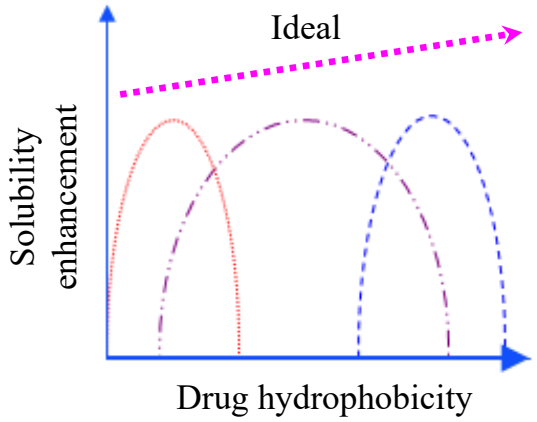
Parrott 2022, Can we predict clinical pharmacokinetics of highly lipophilic compounds by integration of machine learningv

Solubilization Methods for Poorly-Soluble Drugs

Manipulating Solubility by Changing

Solid state properties	Solute-solvent interactions
Particle size	pH control
Polymorphs	Ionic additives
Solvates	Co-solvents
Amorphous forms	Surfactants
	Complexation
	Polymer micelles
	Hydrotropes

Each solubilization method has advantages and limitations.



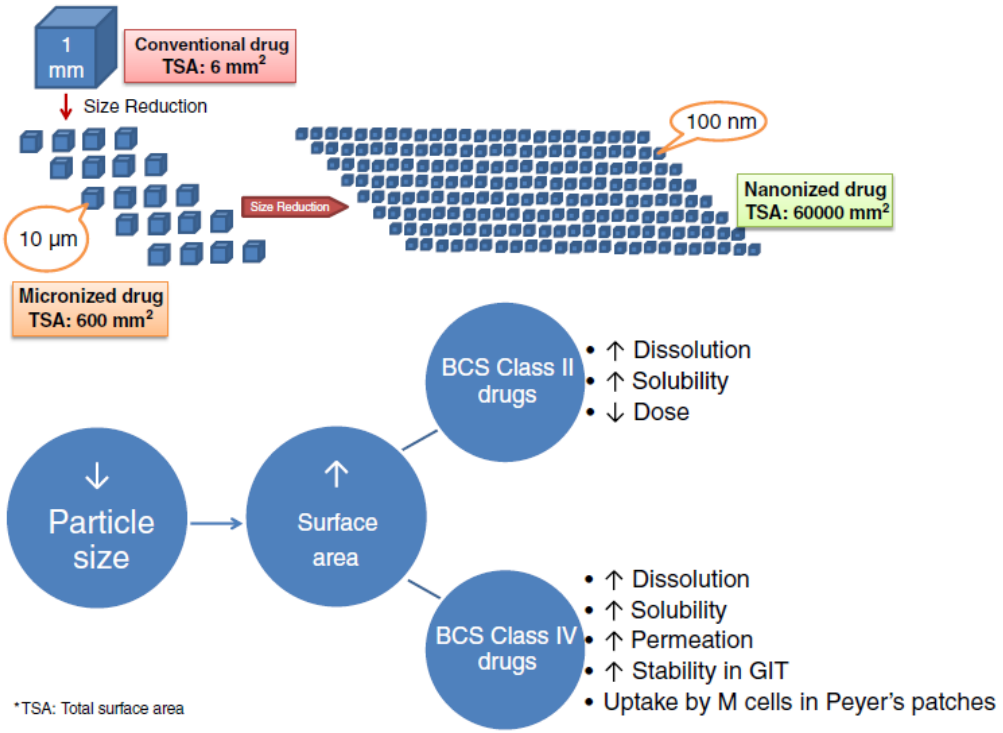
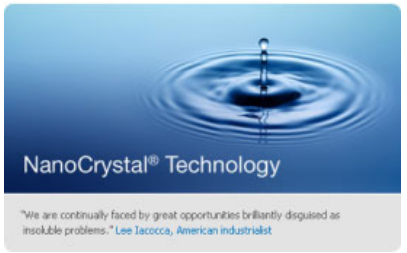


Fig. 6. Mechanistic representation of absorption *via* nanocrystals.

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 (sirolismus, 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

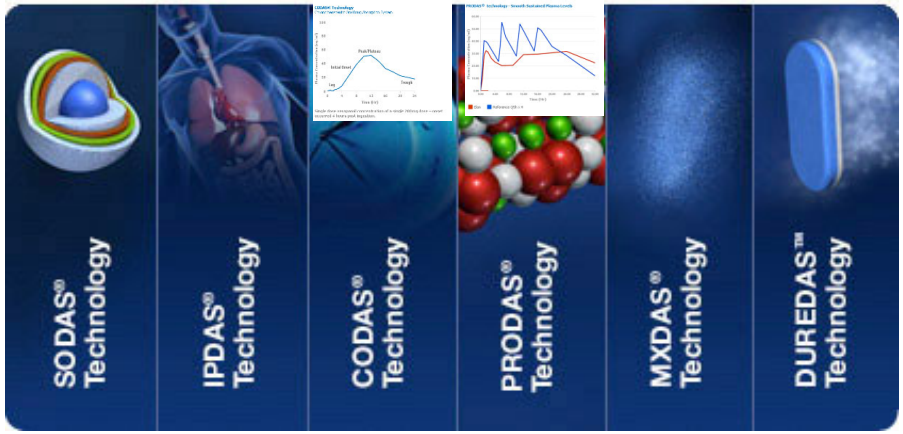
Peltonen, L., J. Hirvonen, Pharmaceutical nanocrystals by nanomilling: critical process parameters, particle fracturing and stabilization methods, J. Pharm. Pharmacol. 62(11) 1569-1579.

Oral Extended release formulations

Spheroidal Oral DAS

Programmable Oral DAS

Dual Release DAS



Intestinal Protective DAS

MatriX Drug Absorption System

24 hour AVINZA® (morphine sulfate extended-release capsules)

Once-Daily NAPRELAN® (naproxen sodium) Controlled-Release Tablets Utilizing the IPDAS® Biphasic System

ONCE-DAILY Focalin® XR® dexmethylphenidate HCl

ampyra® (dalfampridine) D RELEASE TABLETS 10 mg

LUVOX® CR

Ritalin® LA
Methylphenidate HCl

Cardizem CD
Diltiazem HCl

Once at bedtime Controlled onset Verelan® PM (verapamil HCl) extended-release capsules

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

Rapamune (sirolimus) Tablets and Oral Solution — Wyeth 2000

EMEND (aprepitant) — Merck 2003

TriCor 145 mg fenofibrate tablets & 48 mg — Abbott 2004

MEGACE ES megestrol acetate — Par 2005

Triglide (fenofibrate) tablets 50 mg — Skye Pharma 2005

NEW ONCE-MONTHLY INVEGA SUSTENNA paliperidone palmitate extended-release injectable suspension — Janssen 2009

Review article

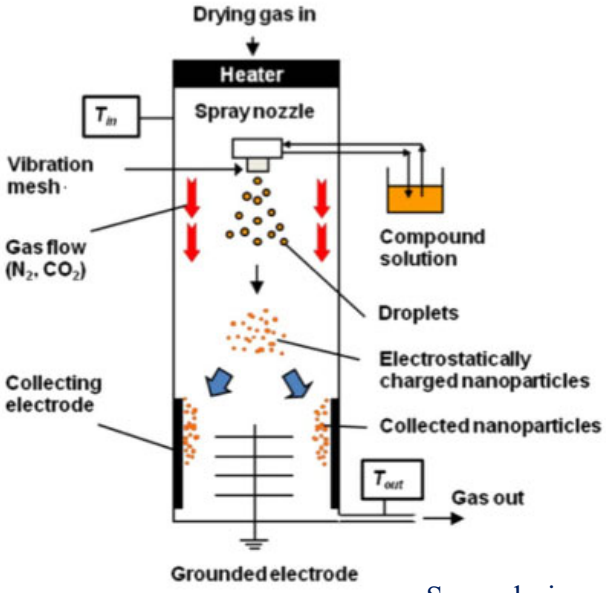
Nanosizing techniques for improving bioavailability of drugs

Raida Al-Kassas*, Mahima Bansal, John Shaw

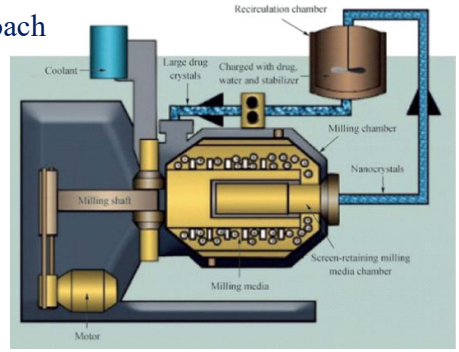
School of Pharmacy, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

Bottom-Up Approach

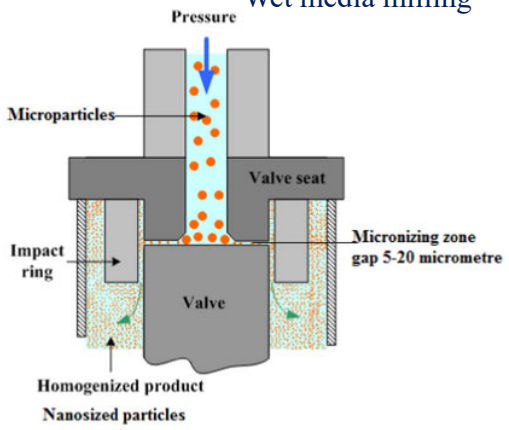
Top-Down Approach



Spray drying



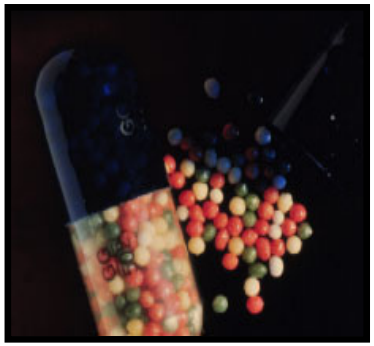
Wet media milling

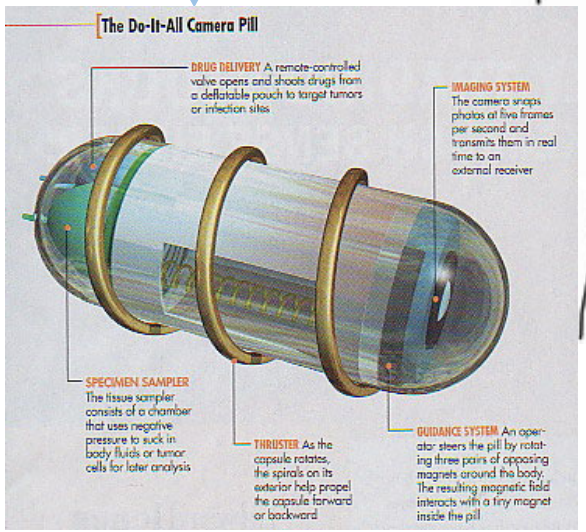


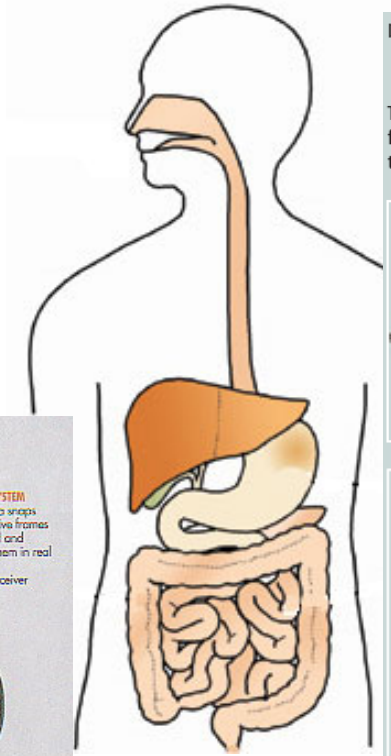
High pressure homogenizer

R. Al-Kassas, M. Bansal, J. Shaw. Nanosizing techniques for improving bioavailability of drugs. Journal of Controlled Release, 260 (2017) 202-212.

Oral Delivery: Targeting to GI Tract







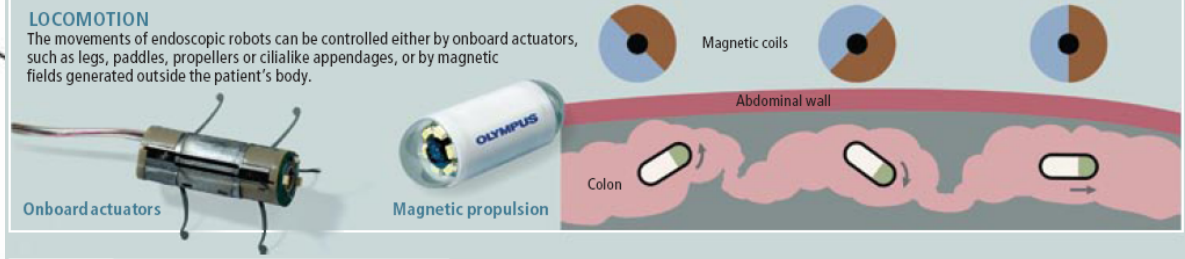
[IN THE WORKS]

MINI BOTS FOR A WIDE RANGE OF JOBS

To make miniature robots that can operate in the digestive tract, engineers must find ways of wirelessly controlling their locomotion and fine movements. And they must fit the required tools, imaging sensors and power supply into a capsule small enough for a patient to swallow. Here are some examples of the diverse tasks engineers want tiny robots to do and the ways they are trying to overcome the technical challenges.

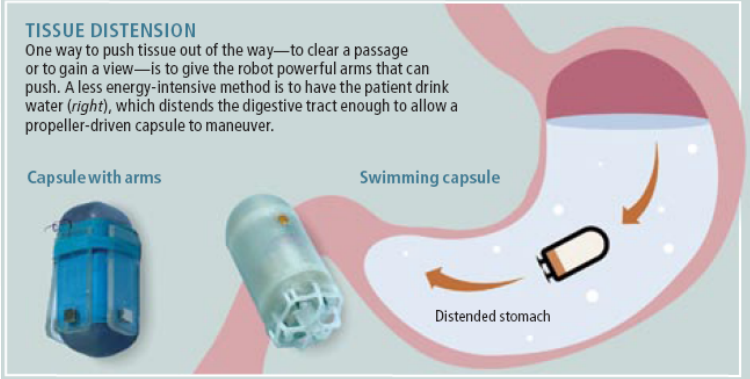
LOCOMOTION

The movements of endoscopic robots can be controlled either by onboard actuators, such as legs, paddles, propellers or cilialike appendages, or by magnetic fields generated outside the patient's body.



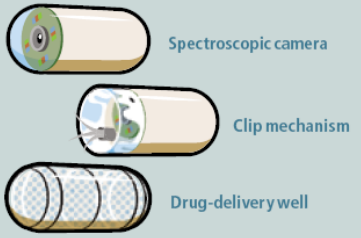
TISSUE DISTENSION

One way to push tissue out of the way—to clear a passage or to gain a view—is to give the robot powerful arms that can push. A less energy-intensive method is to have the patient drink water (*right*), which distends the digestive tract enough to allow a propeller-driven capsule to maneuver.



DIAGNOSIS/TREATMENT

A capsule can carry a wide range of tools: a spectroscopic camera that sees cells underneath the surface layer of tissue; a clip for taking a tissue biopsy; or a well that holds a dose of medication.



Remote control devices

Scientific American. August 2010

Oral Delivery: Gastric Retention Devices

Hwang 1998, Gastric retentive drug delivery systems

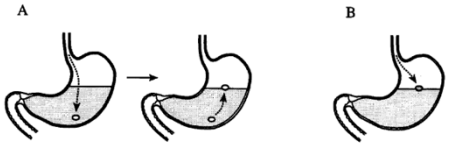


FIGURE 5. Devices with densities lower than 1 can be used to make systems floating in the stomach. The density of a device can be lowered after administration to the stomach (A), or can be made of lower density materials from the beginning (B).

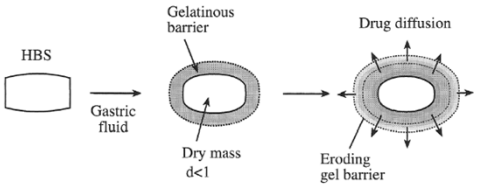


FIGURE 6. Description of the hydrodynamically balanced system (HBS). Diffusion of the gastric fluid to a dried HBS system results in a formation of the gelatinous polymer layer. Drug is released by diffusion and erosion of the gel barrier.

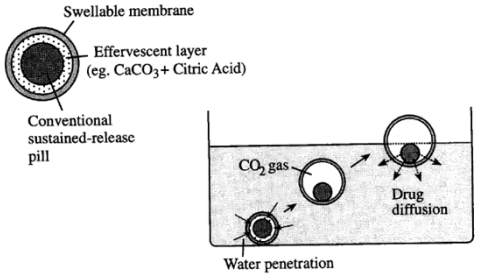


FIGURE 7. Structural characteristics (left) and floating mechanism (right) of the gas-generating microballoon system. The right figure shows penetration of water into the microparticle and generation of CO_2 to make the system float. From Ichikawa.[14]

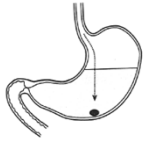


FIGURE 8. Settlement of a high-density device to the bottom of the stomach.

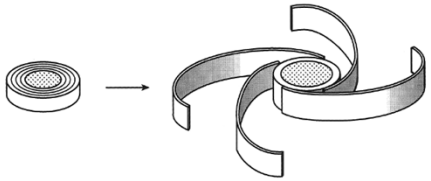


FIGURE 12. The system with the coiled arms (left) can unfold the arms (right) in the stomach. The expanded form is expected to resist gastric retention. From Curatolo and Lo.[107]

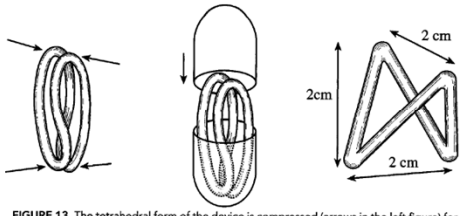


FIGURE 13. The tetrahedral form of the device is compressed (arrows in the left figure) for encapsulation (center). In the stomach, the preferred tetrahedral form (right) is restored for extended gastric retention. From Caldwell et al.[108]

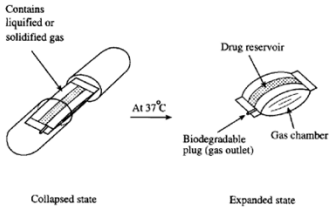


FIGURE 15. An example of an expandable device based on gas evaporation. The expanded device will be deflated upon removal of the plug by biodegradation. From Michaels et al.[118]

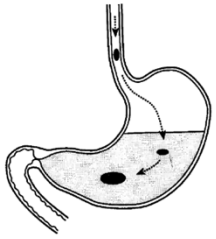


FIGURE 14. The expandable device can swell in the stomach either by absorbing water from the gastric juice or by evaporation of solidified or liquefied gas present in the device.

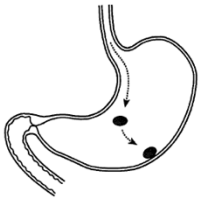


FIGURE 9. Attachment of a mucoadhesive dosage form to the mucus layer in the stomach.

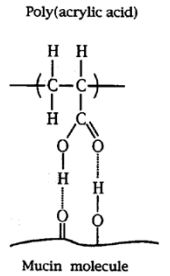


FIGURE 10. Interaction between poly(acrylic acid) and mucin molecules through numerous hydrogen bonding.

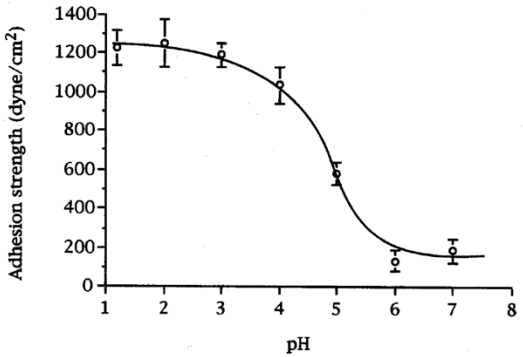


FIGURE 11. Mucoadhesive strength of polycarbophil to rabbit gastric tissue as a function of pH. From Park and Robinson.[97]

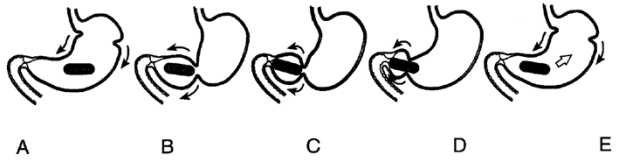


FIGURE 18. A sequence showing the movement of a swollen hydrogel to the pylorus by gastric contractions and retropulsion back to the body of the stomach as visualized by ultrasound and fluoroscopic imaging. From Shalaby et al.[126]

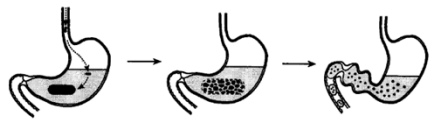


FIGURE 17. A dried superporous hydrogel swells to a huge size in the stomach (A). As the drug is released, the swollen hydrogel can undergo degradation (B) and eventually is emptied from the stomach (C).

Oral Delivery: Gastric Retention Devices

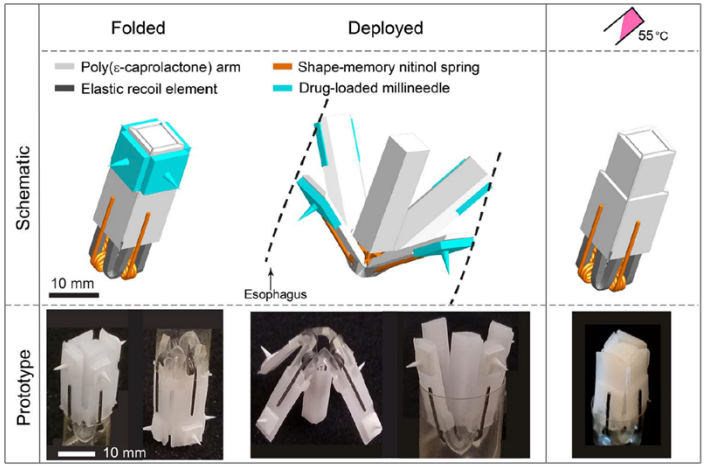


Fig. 2. Esophageal flower-like system. Schematic and prototype images of the flower-like system, illustrating the configurations when folded (before administration), deployed in the esophagus, and folded again following temperature triggering. The components of the design including polymeric arms (light gray), elastic recoil elements (dark gray), nitinol springs (orange), and dissoluble millineedles (green) are shown.

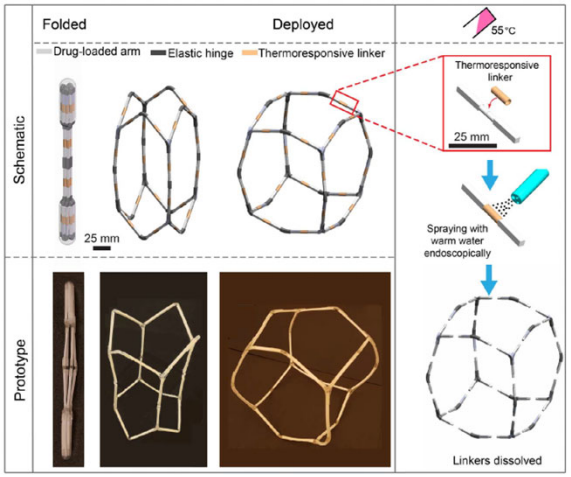
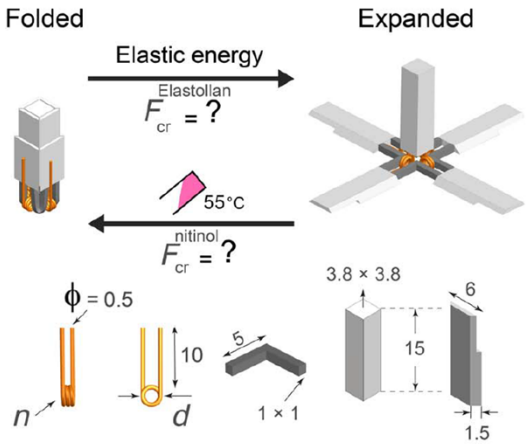
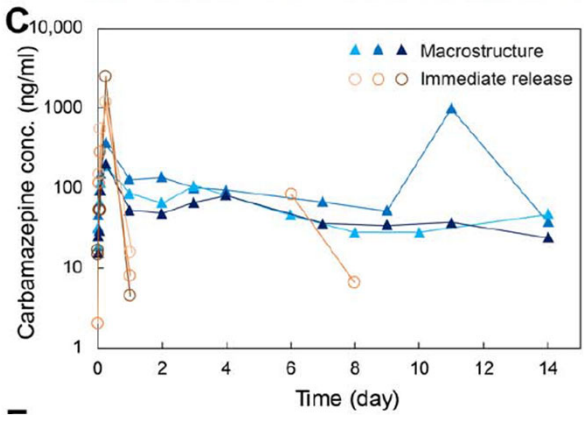


Fig. 4. Flexible mechanical metamaterial as a macrostructure dosage form. The schematic and prototype images of the metamaterial dosage form illustrating the sequence of deployment in stomach and the building components including drug-carrying arms (light gray), elastic hinges (dark gray), and TRLs (orange). The right panel shows temperature-triggered configuration by endoscopically applying warm water (55°C) to trigger the disassembly.

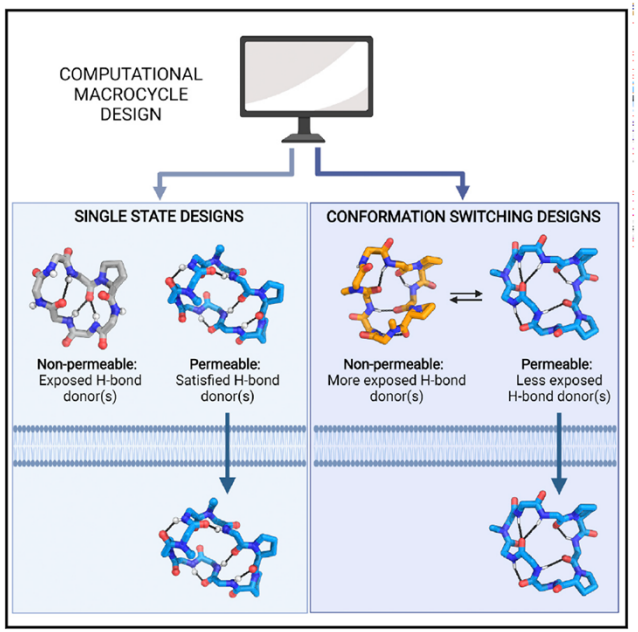


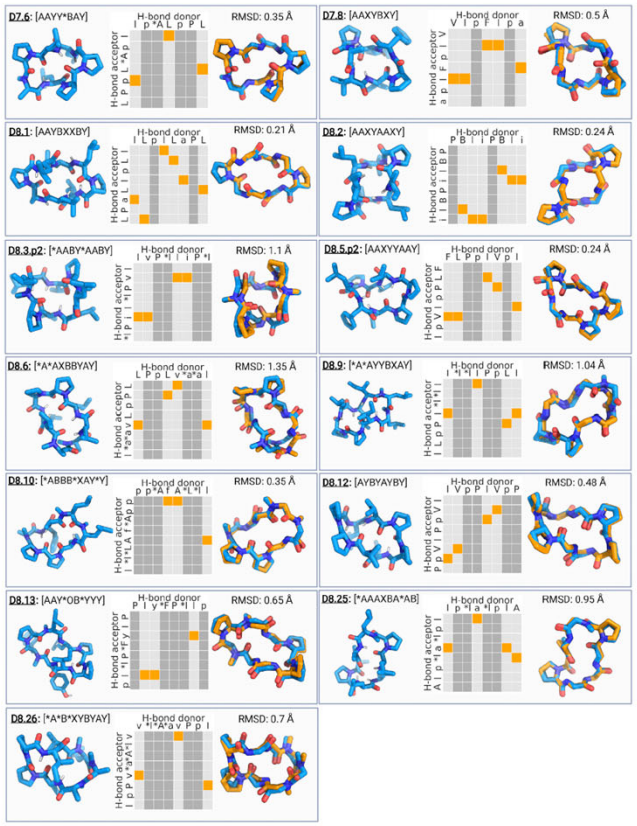


Babaee 2019, Temperature-responsive biometamaterials for gastrointestinal applications

In vivo temperature testing
The temperature in the esophagus and stomach during administration of warm water wasmeasured in a large animal model (three Yorkshire pigs)

Oral Peptide Delivery





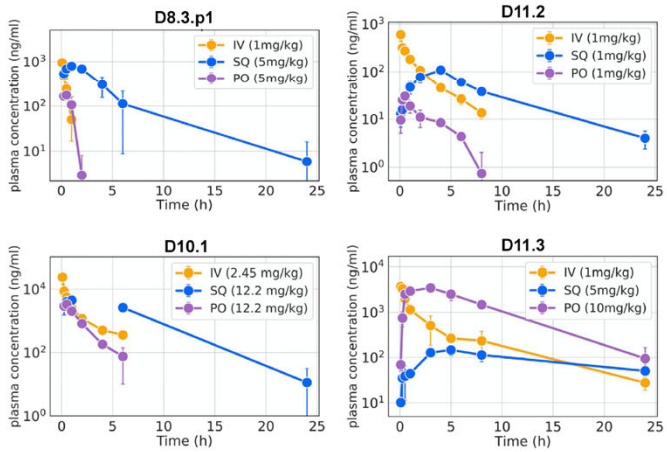


Figure 5. Designed macrocycles are orally bioavailable *in vivo* in rodent models
Plasma concentration of unmodified full-length peptides measured after intravenous (IV), subcutaneous (SQ), and oral (PO) administration in mice (D8.3.p1, D10.1, and D11.3) and rats (D11.2) (n = 3 mice per dosing route for D8.3.p1, D10.1, and D11.3 and n = 3 rats per dosing route for D11.2). D8.3.p1 and D10.1 were studied in female BALB/c mice, D11.2 was studied in male Sprague Dawley (SD) rats, and D11.3 was studied in male swiss albino mice.
See also Data S5.

Bhardwaj 2022, Accurate de novo design of membrane-traversing macrocycles

Oral Delivery: Biotherapeutics

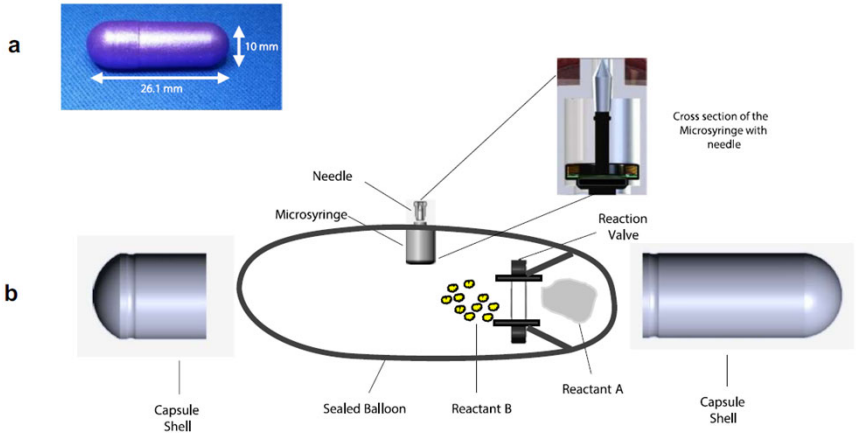
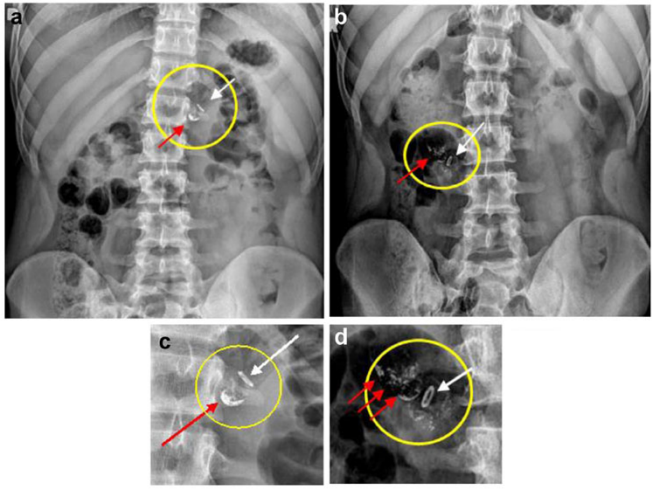
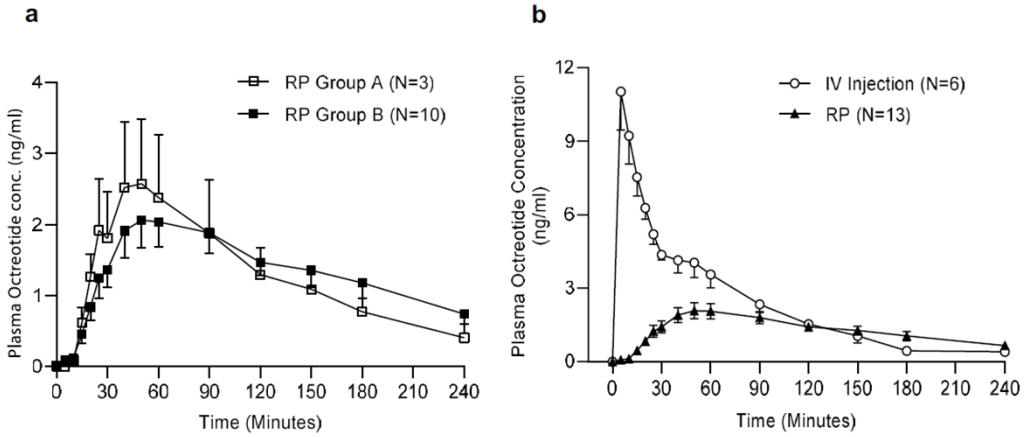


Fig. 1 RP design. **a** Fully assembled enteric-coated RP. **b** Schematic drawing showing various parts and components of the RP. Inset shows the microsyringe containing the needle with the drug microtablet which gets injected into the jejunal wall. The microtablet and needle are aseptically manufactured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

Fig. 3 **a** Representative X-ray image of an intact RP residing in the stomach (encircled) showing a radio-opaque ring (which is part of the device) at one end of the device (white arrow) and barium sulfate powder inside the capsule shell at the other end (red arrow). **b** Representative X-ray image of a deployed RP in the small intestine (encircled). The radio-opaque ring (white arrow) is part of the device whereas barium sulfate is dispersed inside the intestinal lumen (red arrows). **c** Magnified encircled area from **a**. **d** Magnified encircled area from **b**





PK parameters for Octreotide administered via IV injection and RP

Group	C_{max} (ng/mL)	T_{max} (min)	$AUC_{last/Dose}$ ((min*ng/mL)/(μg/kg))	Bioavailability (% F)
IV Sandostatin (N=6)	11.1 ± 1.6	5	389 ± 22	NA
RP (N=13)	2.4 ± 0.3	50	226 ± 30	65 ± 9

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 ± SE

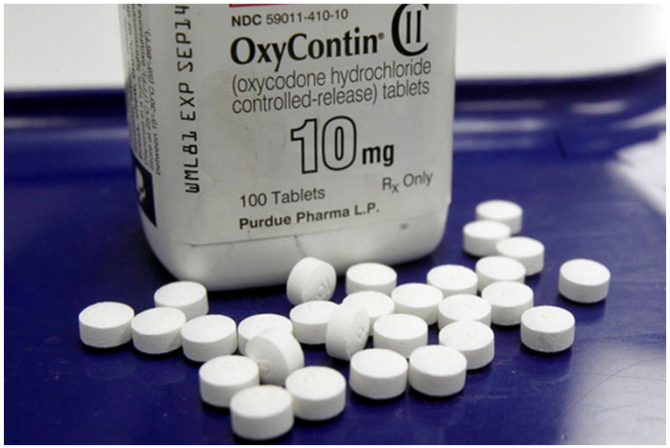
Dhalla 2022, A robotic pill for oral delivery of biotherapeutics

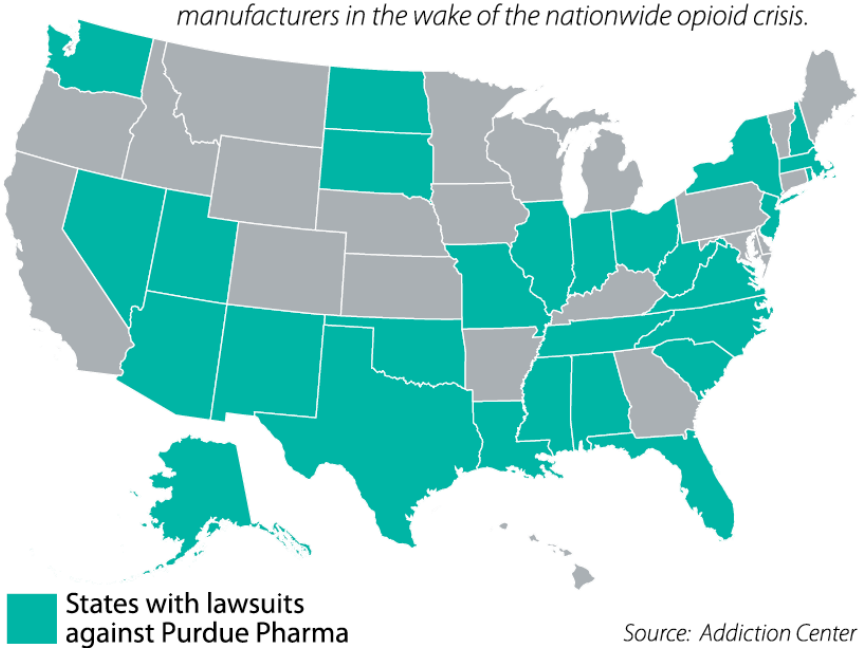
Opioid Use Disorder & Purdue Pharma

https://www.nytimes.com/2021/12/16/health/purdue-pharma-opioid-settlement.html

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.



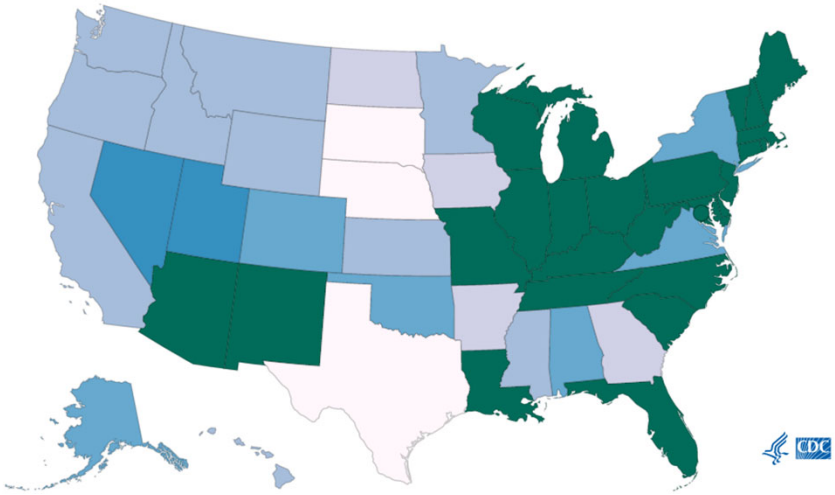


https://www.theindianalawyer.com/articles/48769-citing-opioids-devastation-state-sues-purdue-pharma

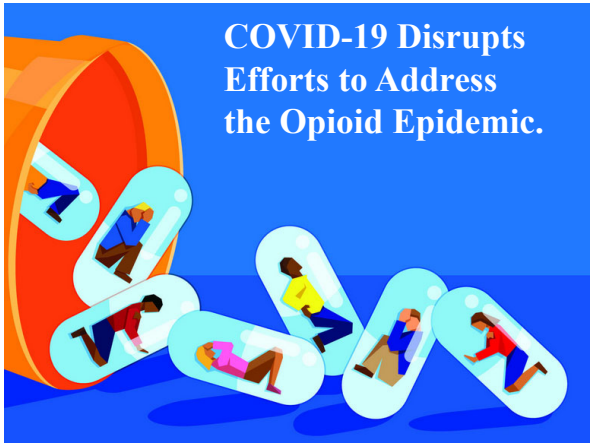
Purdue Pharma is NOT related to Purdue University

Opioid Use Disorder & Abuse-Deterrent Formulations

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



https://www.cdc.gov/drugoverdose/deaths/2019.html



https://www.ravemobilesafety.com/blog/the-opioid-crisis-and-covid-19

> *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.*
>
> DR. TIM K. BRENNAN
> DIRECTOR, ADDICTION INSTITUTE AT MOUNT SINAI WEST

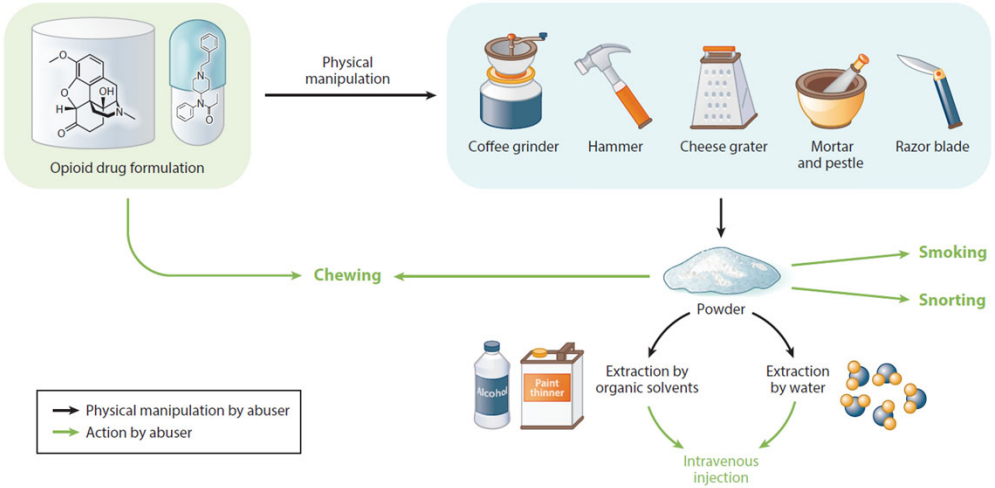


Figure 1

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. The powders can be further treated with water or organic solvents to extract opioids for intravenous injection.

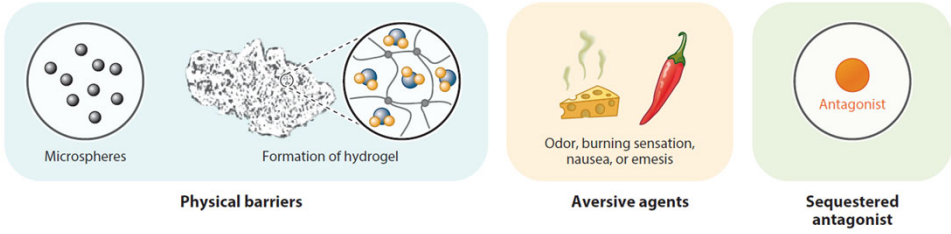


Figure 2

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.

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

Transdermal Drug Delivery Systems

Transdermal Drug Delivery Systems

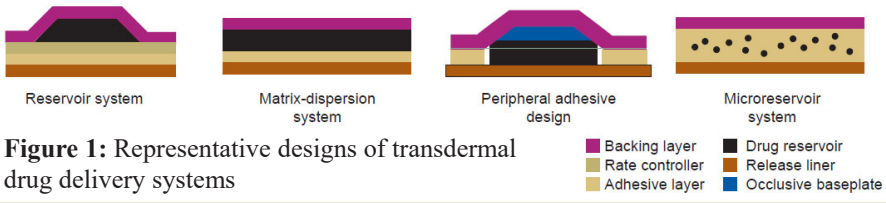


Figure 1: Representative designs of transdermal drug delivery systems

S. Kandavilli,V. Nair, and R. Panchagnula. Polymers in transdermal drug delivery systems. Pharm. Tech. May: 62-80, 2002

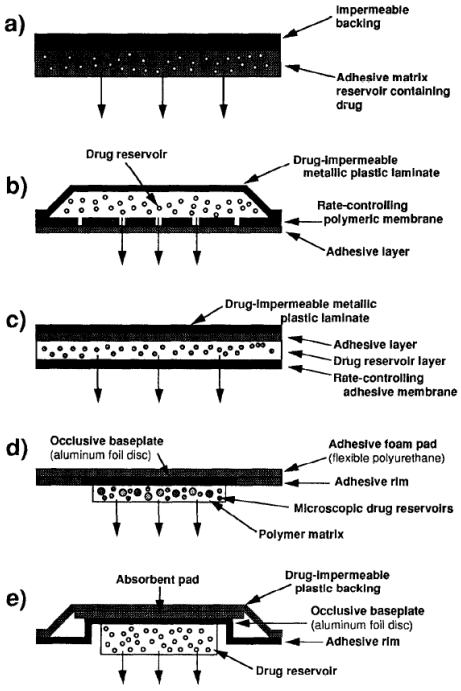


Fig. 1 Cross-sectional view of several TDS:
(a) pressure-sensitive adhesive (PSA) matrix device;
(b) membrane-moderated TDS;
(c) adhesive-controlled TDS;
(d) microreservoir-type TDS;
(e) matrix dispersion-type TDS.

K. Sugibayashi and Y. Morimoto. Polymers for transdermal drug delivery systems. J. Control. Release 29 (1994) 177-185.

PLGA Nanofibers for Transdermal Delivery

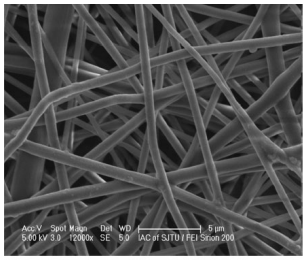


Fig. 3. SEM morphology of Daidzein-NLCs-Azone-nanofibers.

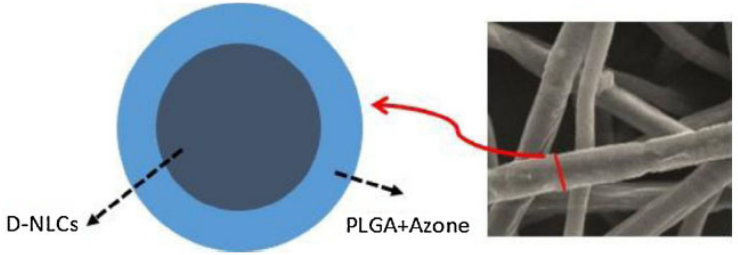


Fig. 4. Schematic figure of cross-sectional view of D-NLCs-Azone-nanofibers.

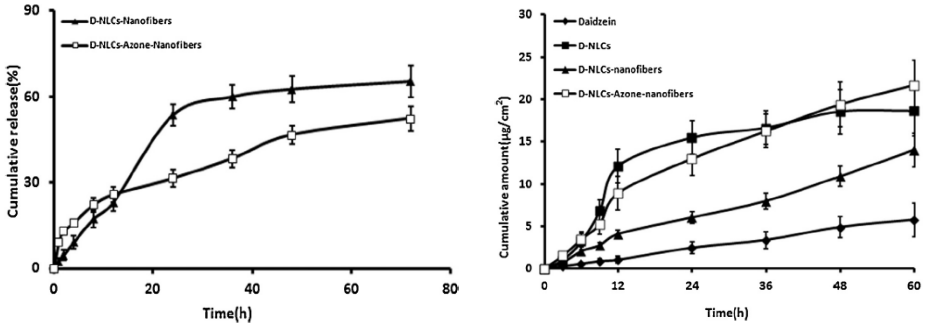
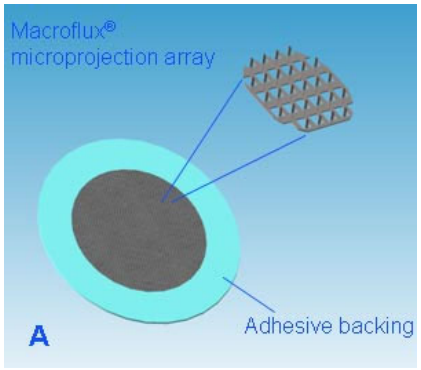
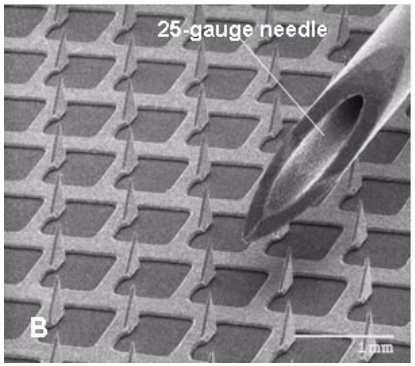


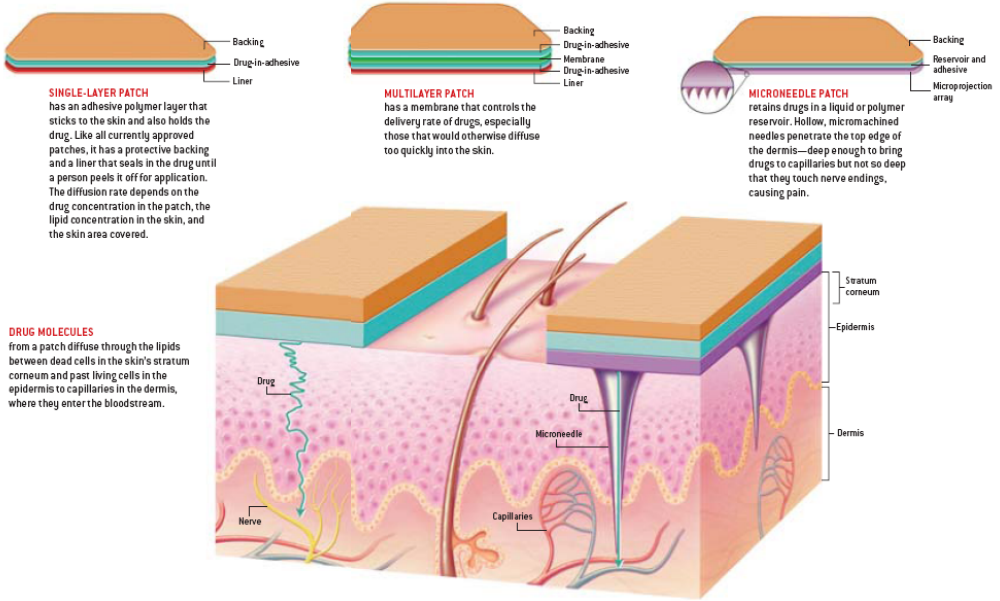
Fig. 5. In vitro release profile of daidzein from D-NLCs-Nanofibers and D-NLCs- Azone-Nanofibers in Phosphate Buffered Saline (pH 7.4). Keys: (▲) D-NLCs- Nanofibers, (□) D-NLCs-Azone-Nanofibers. Each value represents the mean±SD (n = 3).

J. Song, X. Fan, Q. Shen. Daidzein-loaded nanostructured lipid carriers-PLGA nanofibers for transdermal delivery. International Journal of Pharmaceutics 501 (2016) 245-252.

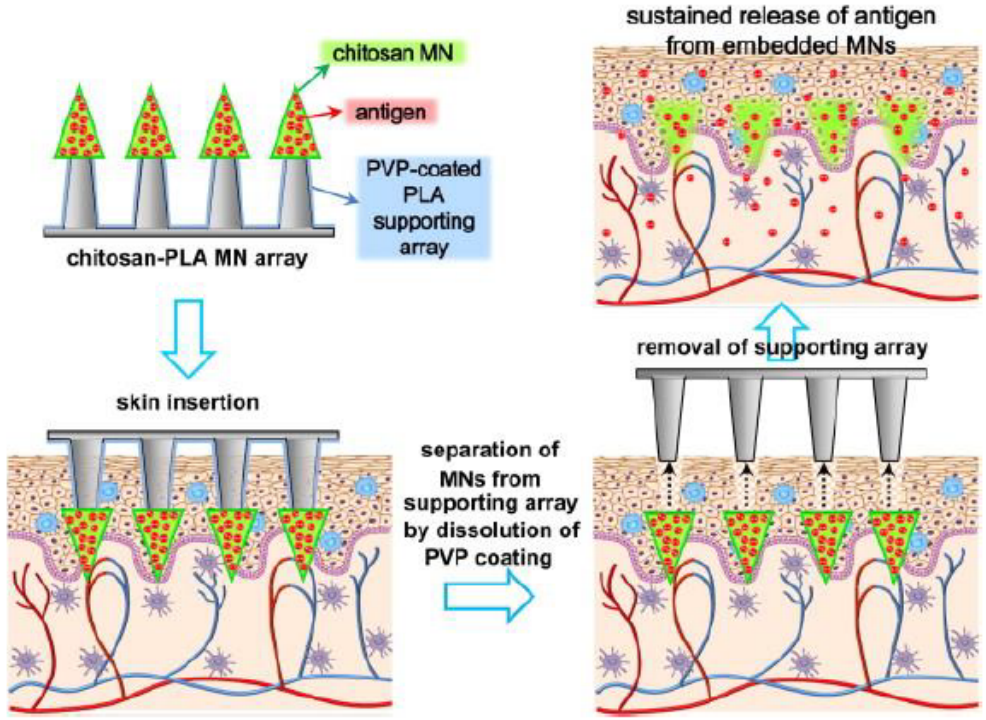
Transdermal Patches with Microneedles







Scientific American. April 2003



Chen, M.-C., Huang, S.-F., Lai, K.-Y., Ling, M.-H.: Fully embeddable chitosan microneedles as a sustained release depot for intradermal vaccination. Biomaterials 34(12): 3077-3086, 2013.

Microneedle Transdermal Drug Delivery

Phase-Transition Microneedle Patches

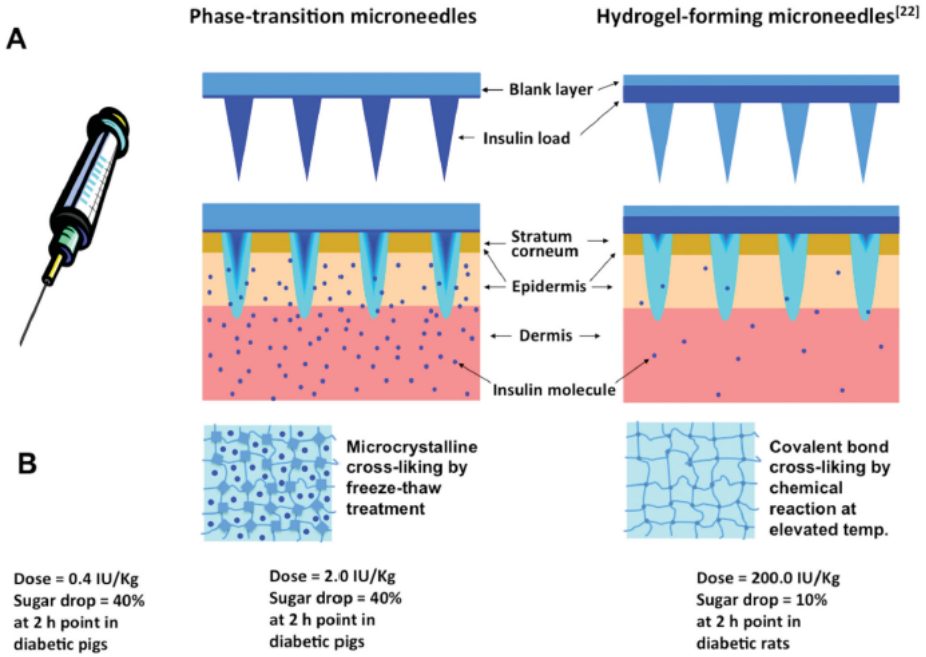


Figure 1. Working principle and fabrication process of PTM patches.
A) The microneedles absorb the bodily fluid from the dermis layer to convert form hard glassy state to hydrogel state to allow the preloaded insulin to release to the bodily fluid in the dermis layer.
B) The microneedle matrix of PTM 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.

Sixing Yang, Fei Wu, Jianguo Liu, Guorong Fan, William Welsh, Hua Zhu, Tuo Jin:
Phase-Transition Microneedle Patches for Efficient and Accurate Transdermal Delivery of Insulin.
Adv. Funct. Mater. 25 (29): 4633-4641, 2015.

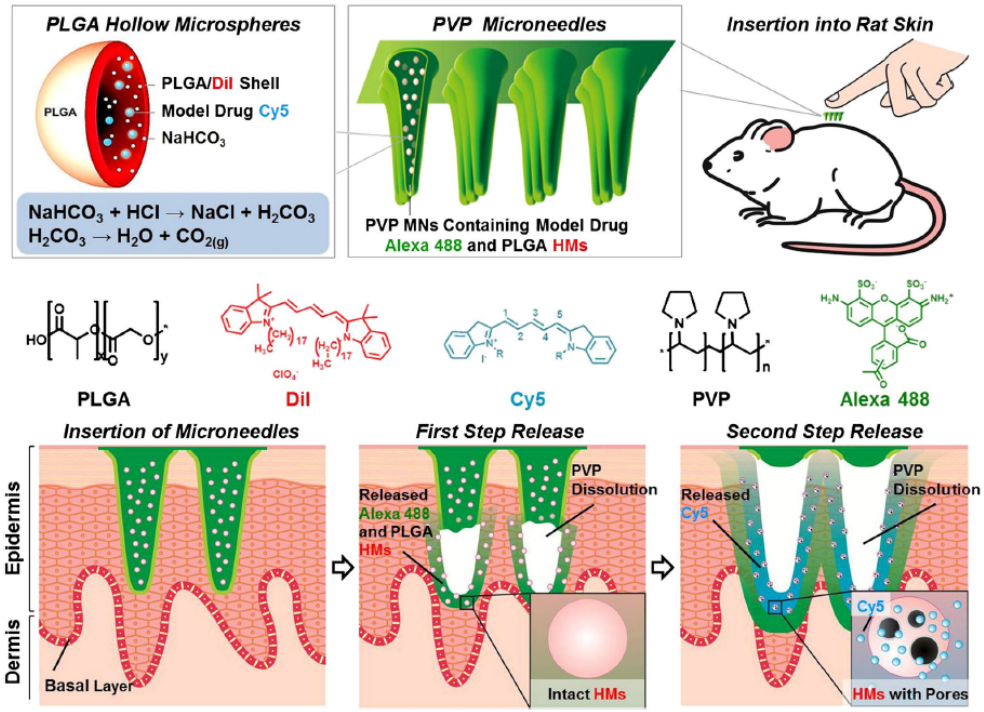


Fig. 2 Schematic illustration of the design of PVP MN arrays containing pH-responsive PLGA HMs and their mechanism for codelivery of two different model drugs Alexa 488 and Cy5 in sequence transdermally. After insertion into skin, the first step of rapid release of Alexa 488 and DiI-labeled HMs was accomplished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

Naves 2017, Poly(lactic-co-glycolic) acid drug delivery systems through transdermal pathway: an overview. Prog. Biomater. 6:1-11, 2017.

Polymeric Microneedles for Transdermal Protein Delivery

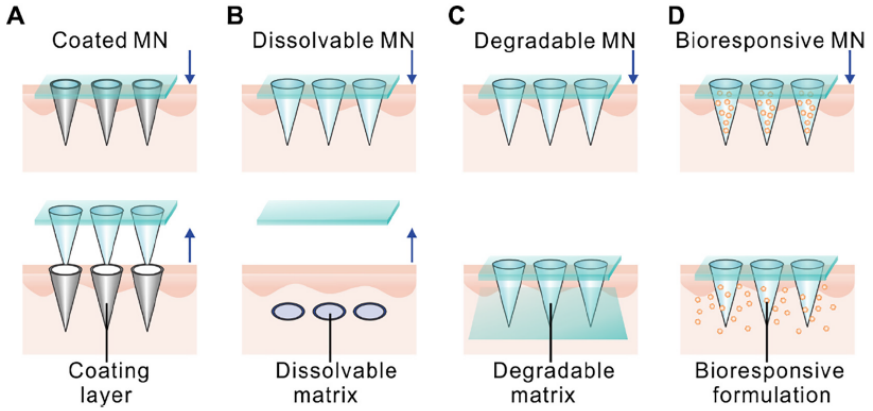
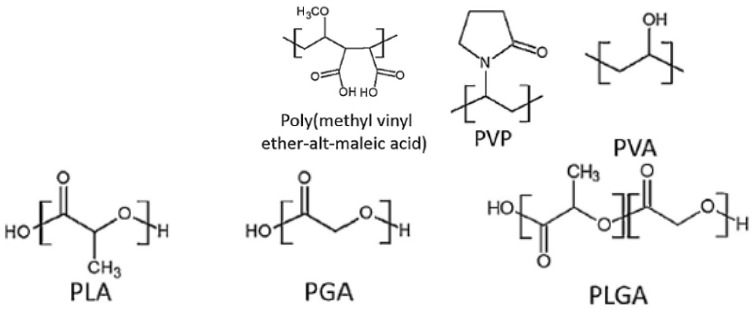


Fig. 1. Representative types of polymeric MNs for protein delivery. A) Solid MNs coated with polymeric drug formulation on the MNs surface for direct delivery. B) Dissolvable polymeric MNs that remain in the skin and dissolve to deliver the drug encapsulated within. C) Degradable polymeric MNs that remain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

Y. Ye, J. Yu, D. Wen, A.R. Kahkoska, Z. Gu. Polymeric microneedles for transdermal protein delivery. Advanced Drug Delivery Reviews 127 (2018) 106-118.



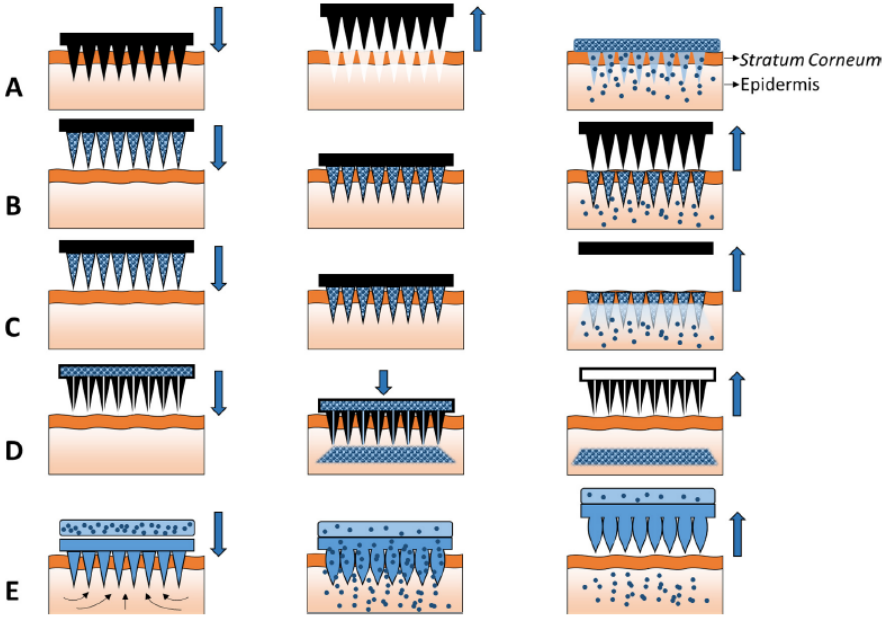


Fig. 1. A schematic representation of five different MN types used to facilitate drug delivery transdermally. (A) Solid MNs for increasing the permeability of a drug formulation by creating micro-holes across the skin. (B) Coated MNs for rapid dissolution of the coated drug into the skin. (C) Dissolvable MNs for rapid or controlled release of the drug incorporated within the microneedles. (D) Hollow MNs used to puncture the skin and enable release of a liquid drug following active infusion or diffusion of the formulation through the needle bores. (E) Hydrogel forming MNs take up interstitial fluids from the tissue, inducing diffusion of the drug located in a patch through the swollen microprojections.

Larraneta 2016, Microneedle arrays as transdermal and intradermal drug delivery systems: Materials science, manufacture and commercial development. Mater. Sci. Eng. R 104 (2016) 1-32

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

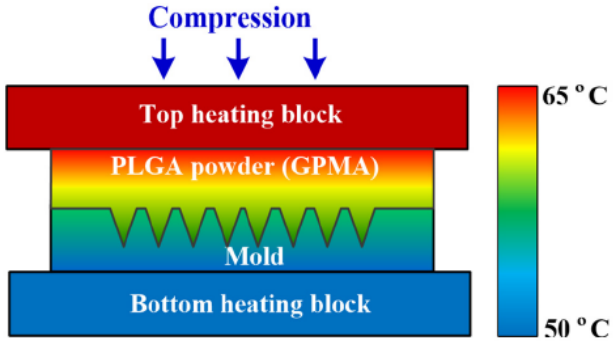
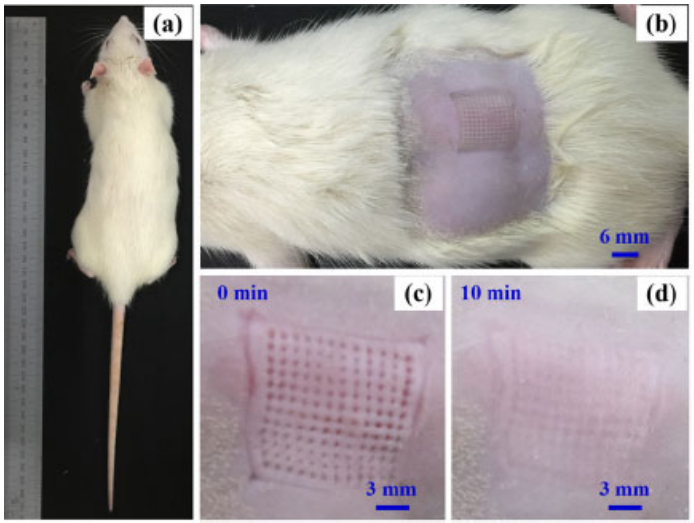


Fig. 1. Schematic of modified hot embossing setup for the GMPA fabrication.



J. Li, Y. Zhou, J. Yang, R. Ye, J. Gao, L. Ren, B. Liu, L. Liang, L. Jiang. Fabrication of gradient porous microneedle array by modified hot embossing for transdermal drug delivery. Materials Science and Engineering: C 96 (2019) 576-582

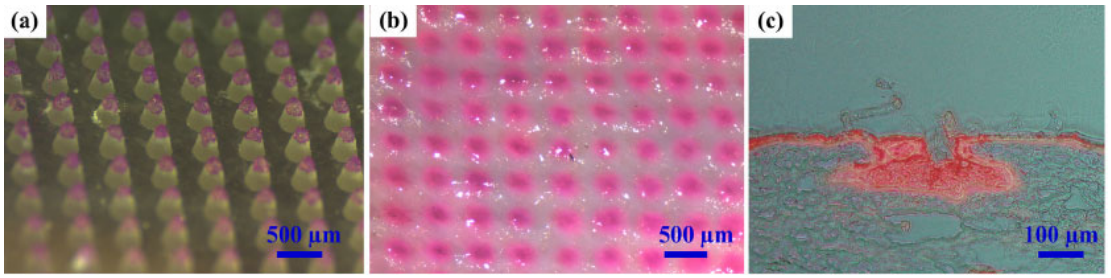


Fig. 6. (a) GPMA loaded with dried Rhodamine B at microneedle tips, (b) rabbit skin punctured by GPMA, and (c) drug diffusion image of punctured skin slice.

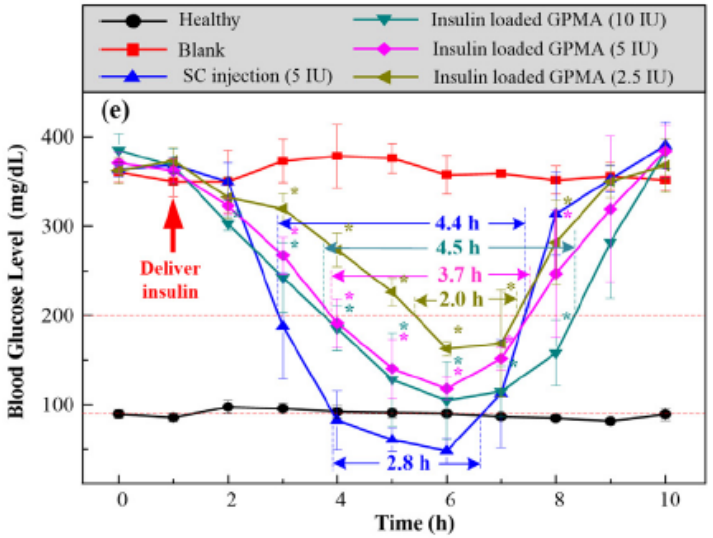
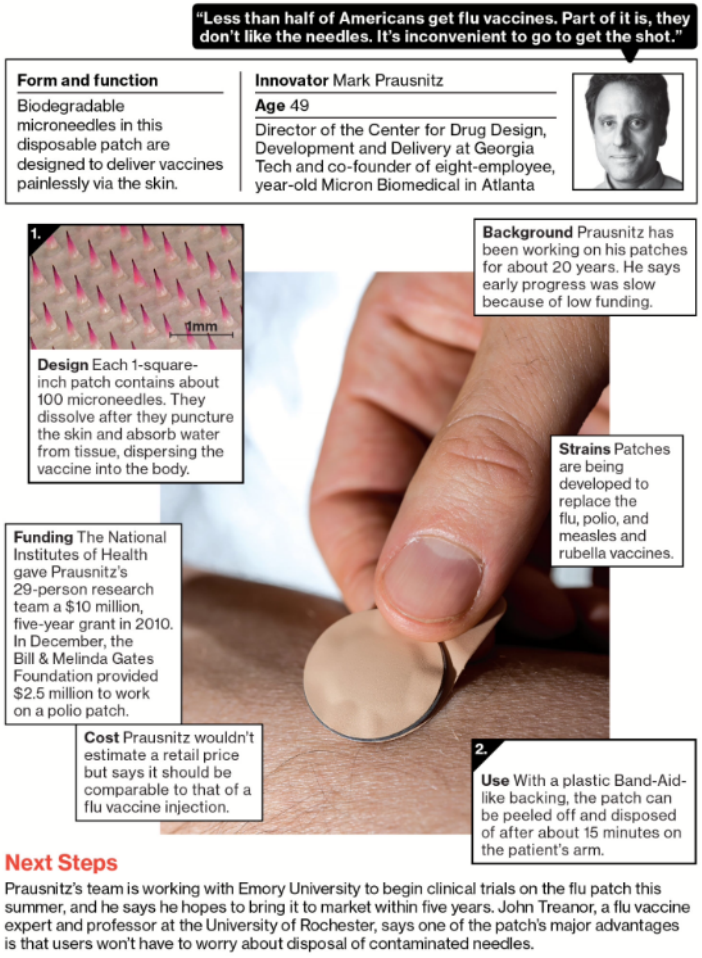


Fig. 7. Transdermal insulin delivery in diabetic rats: (a) diabetic SD rats with a weight of approximately 200 ± 20 g were selected, (b) SD rat treated with GPMA patch, (c-d) skin recovery process after removing the GPMA, and (e) BGLs in diabetic rats after transdermal administration of insulin-loaded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

Transdermal Vaccine Patches

Vaccine Patch: Vaccination without needles, the best idea ever
By Caroline Winter. Bloomberg Businessweek. May 18, 2015

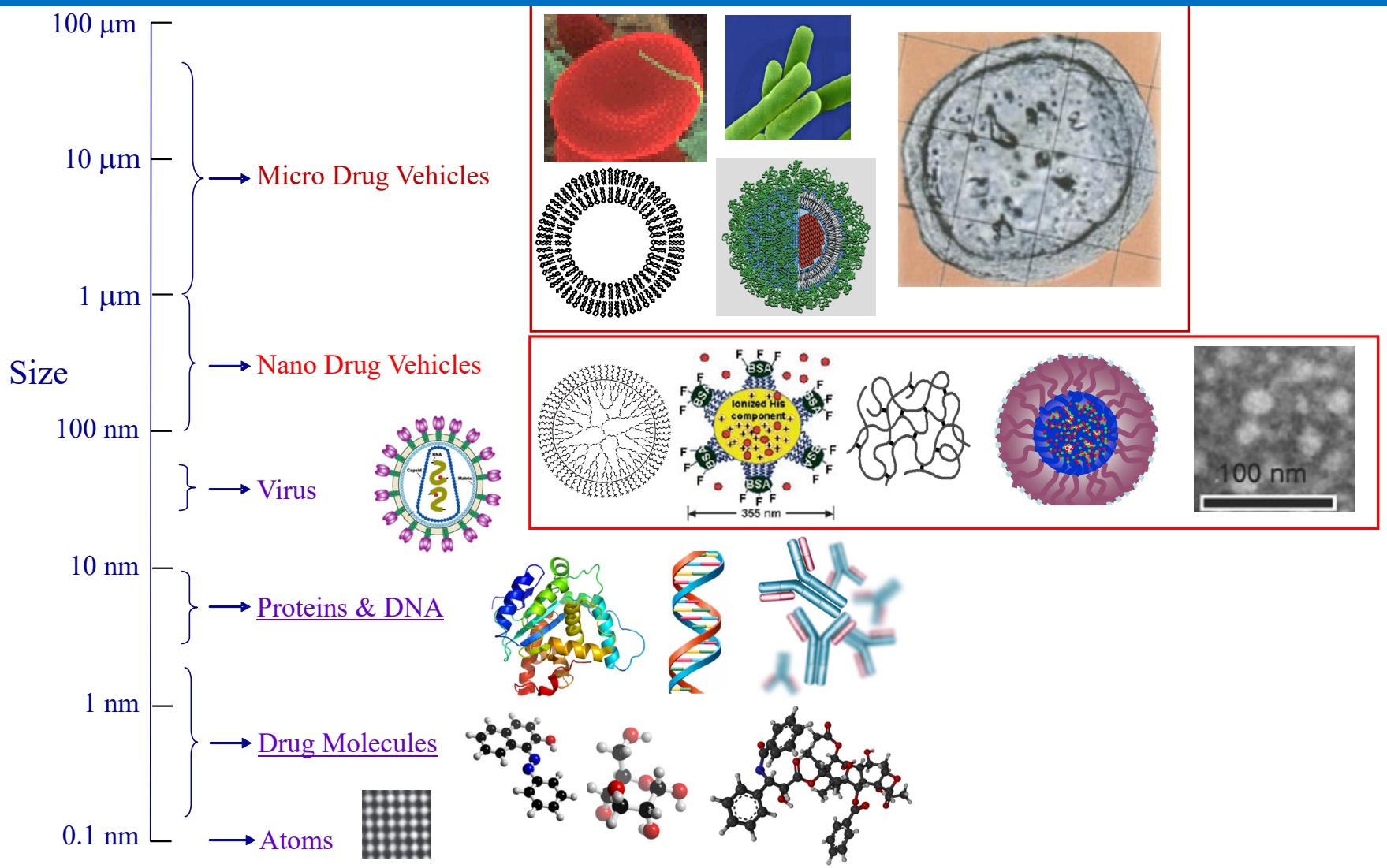


Medicinal Patches

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



Methods for Making Nano/Micro Particle

1. Emulsion methods (W/O/W, S/O/W, W/O/O, S/O/O)

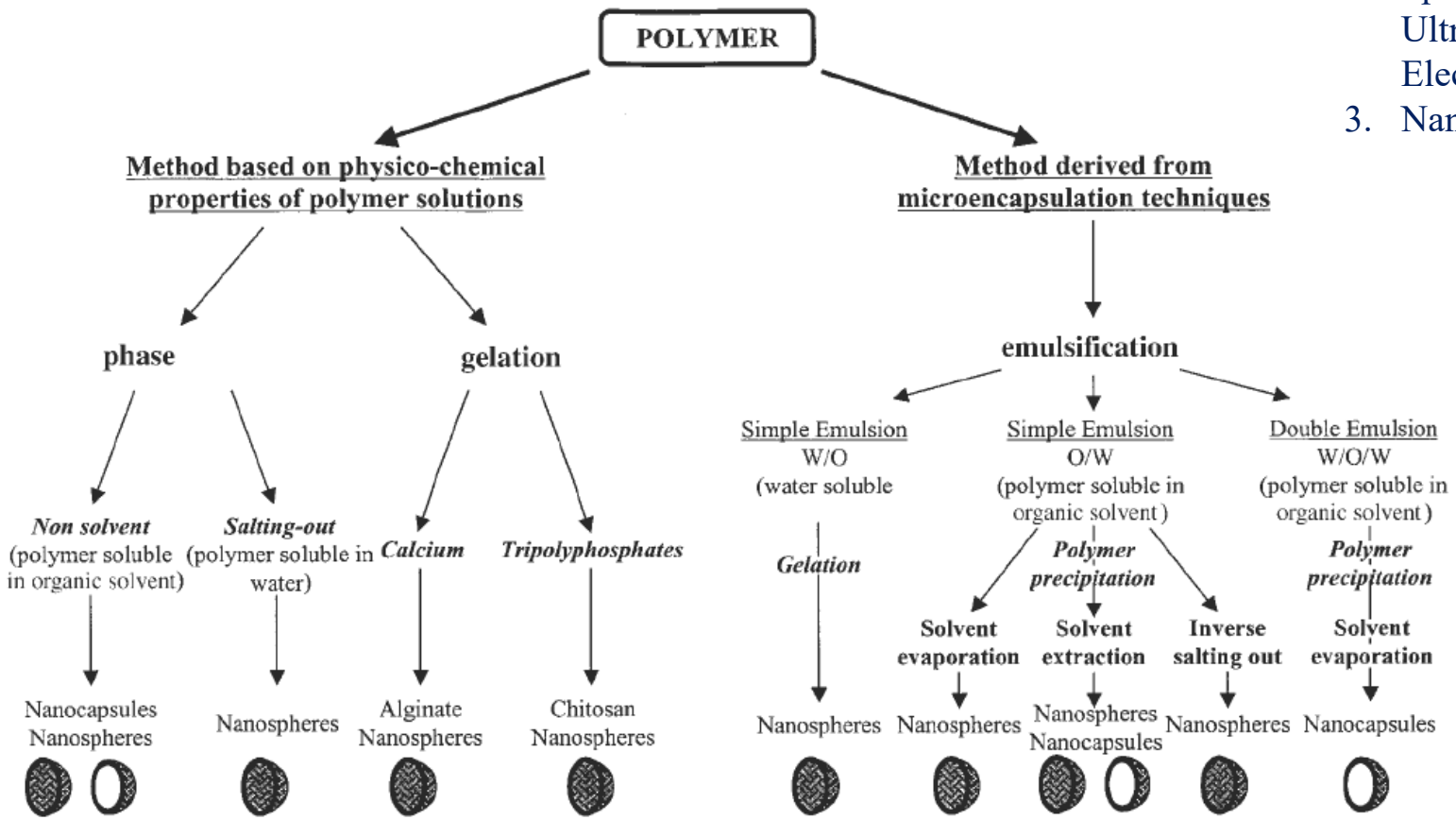


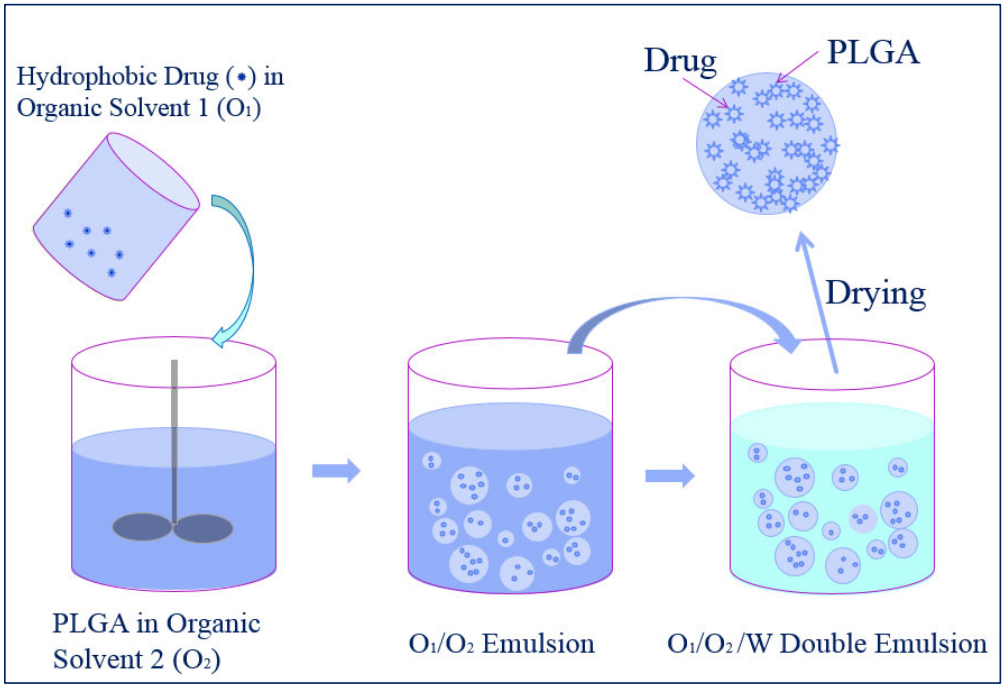
Fig. 3 Summary of the different methods to prepare nanospheres and nanocapsules from a polymer. W/O: water-in-oil, O/W: oil-in-water, W/O/W: water-in-oil-in-water.

2. Atomization methods
   Spray drying, spray freeze-drying
   Ultrasonic atomization
   Electrospray
3. Nano/micro fabrication

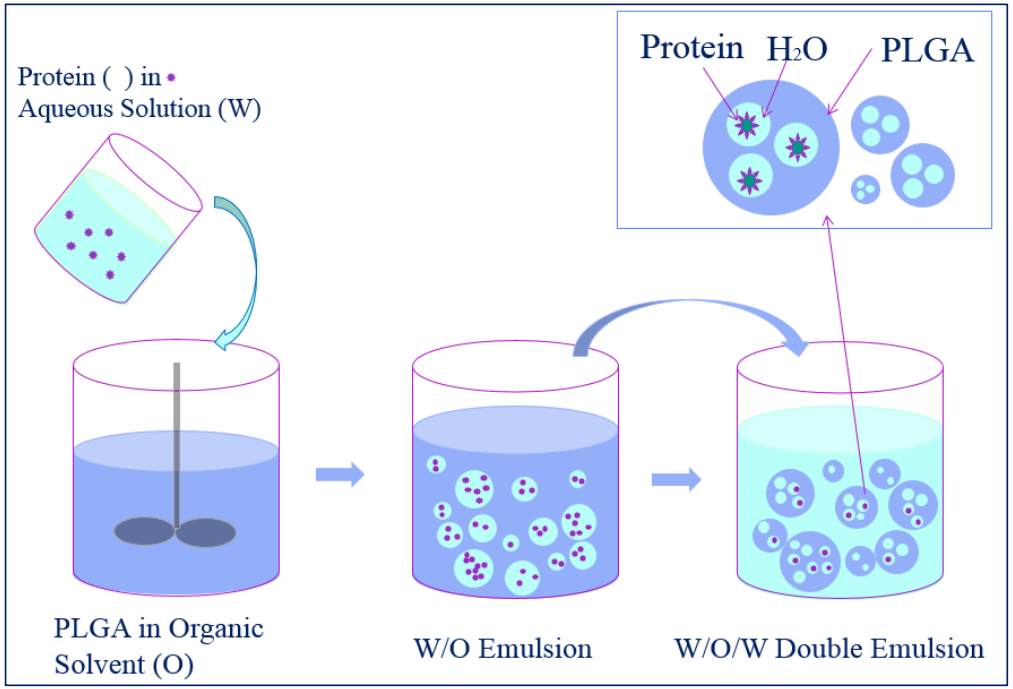
Fattal, E. and Vauthier, C. Encyclopedia of Pharmaceutical Technology, pp. 1864-1882, 2002.

Double Emulsion Methods for Microparticle Preparation

Small Hydrophobic Drugs

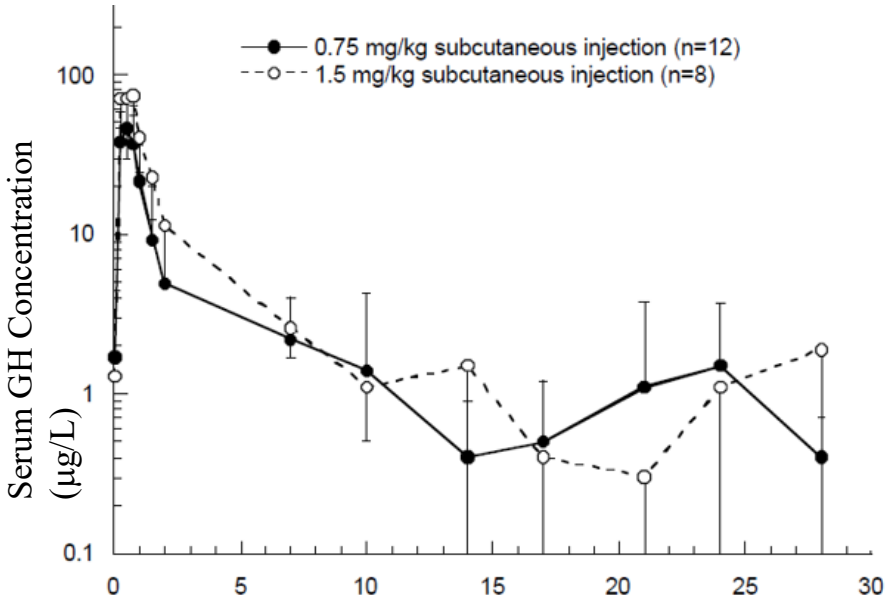


Peptide and Protein Drugs



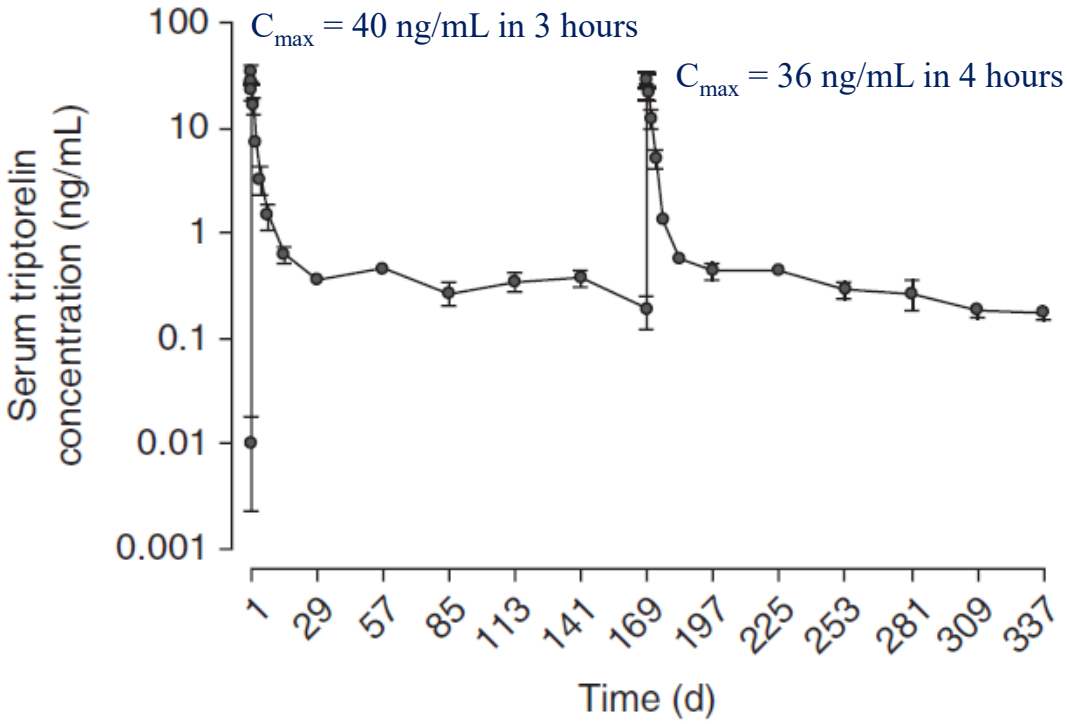
Pharmacokinetic Profiles of Long-Acting Formulations

Nutropin Depot™
Somatotropin (rDNA origin) for injectable suspension



Single dose mean GH concentration in pediatric GHD patients

Trelstar Suspension™
Somatotropin (rDNA origin) for injectable suspension



Triptorelin 6-month formulation in the management of patients with locally advanced and metastatic prostate cancer. An open-label non-comparative, multicenter, Phase III study.
Clin. Drug. Investig. 29 (12): 757-765, 3009

Injectable Long-Acting Formulations Approved by the FDA

LupronDepot (leuprolide acetate for depot suspension)
1, 3, 4, 6 months, MP
1989, 1996, 1997, 2011
7.5 mg/month

TRELSTAR (triptorelin pamoate for injectable suspension)
1, 3, 6 months, MP
2000, 2001, 2010
3.75 mg/month

Vivitrol (naltrexone for extended-release injectable suspension)
1 month MP, 2006
380 mg/month

Signifor LAR (pasireotide) for injectable suspension
1 month, MP, 2014
20, 40, 60 mg/month

Lutrate Depot
(Leuprolide acetate)
3 months MP, 2018
22.5 mg/month

Zoladex 3-MONTH 10.8 mg DEPOT
GOSERELIN ACETATE IMPLANT
1, 3 months SI, 1989
3.6 mg/month

Somatulin LA
(Lanreotide acetate)
2 weeks MP, 2000
30 mg/2 weeks

Ozurdex (dexamethasone intravitreal implant) 0.7 mg
3 months SI, 2009
0.7 mg/3 months

Triptodur (triptorelin) for extended release injectable suspension
6 months MP, 2017
22.5 mg/6 months

SCENESSE
(Afamelanotide Implant)
2 months SI, 2019
8 mg/month

Sandostatin LAR Depot (octreotide acetate for injectable suspension)
1 month MP ,1998
20 mg/month

Arestin minocycline HCl 1mg MICROSPHERES
2 weeks MP ,2001
1 mg/2 weeks

PROPEL
MOMETASONE FUROATE IMPLANT
1 month SI, 2011
0.37 mg/month

Zilretta triamcinolone acetonide extended release injectable suspension 32 mg
3 months MP, 2017
32 mg/3 months

DURYSTA (bimatoprost implant) 10 mcg
4-6 months SI, 2020
10 µg/6 months

ATRIDOX (doxycycline hyclate) 10%
Cost Effective
1 week, IS ,1998
50 mg/week

Eligard (leuprolide acetate for injectable suspension)
1, 3, 4, 6 months IS, 2002
7.5 mg/month

Once-weekly **BYDUREON BCise**
1 week MP, 2012, 2017 (BCise)
2 mg/week

Sublocade (buprenorphine extended-release)
1 month IS, 2017
100, 300 mg/month

Nutropin DEPOT (somatropin (rDNA origin) for injectable suspension)
1 month MP, 1999
13.5 mg/month (Discontinued)

RisperdalCONSTA risperidone Long-Acting Injection
2 weeks MP, 2003
25 mg/2 weeks

Lupaneta Pack
leuprolide acetate for depot suspension, 11.25 mg for intramuscular injection and norethindrone acetate tablets, 5 mg for oral administration
3 month MP ,2012
3.75 mg/month

once-monthly **PERSERIS** (risperidone)
1 month IS, 2018
90, 120 mg/month

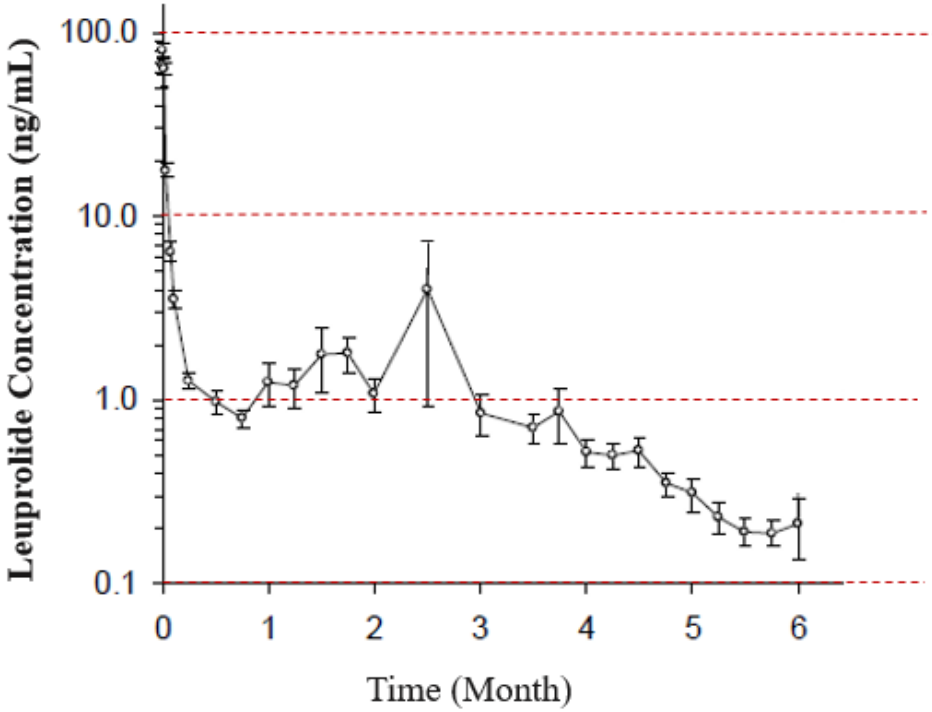
MP: Microparticle
SI: Solid implant
IS: In Situ forming implant

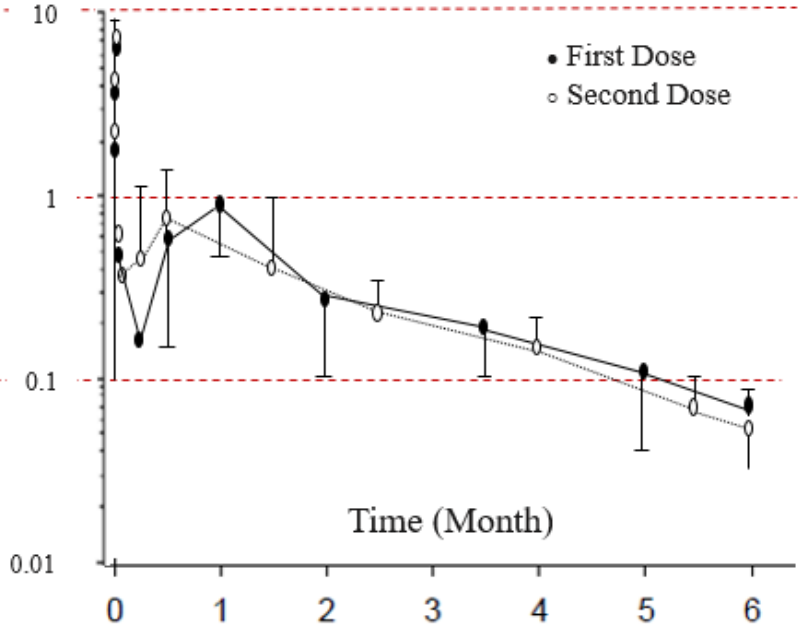
Pharmacokinetic Profiles of Long-Acting Formulations

A. Eligard®

Lupron®

45 mg / 6 months



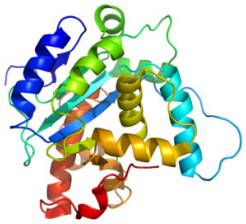


Pharmacokinetic/pharmacodynamic response.

Concentration-time profiles.

Issues with Delivery of Biopharmaceuticals

Protein Formulations



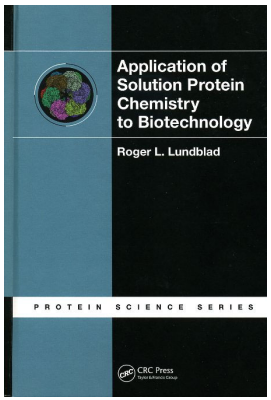
Proteins: Tertiary structures

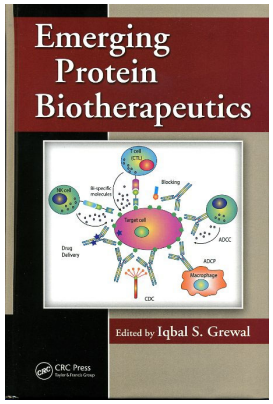
Factors to consider for formulation:
- Loading capacity
- Encapsulation efficiency
- Release profiles → *In vitro & in vivo* correlation
- Protein stability → Bioactivity

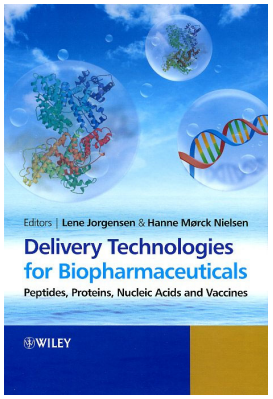
Polymers: Biodegradable polymers

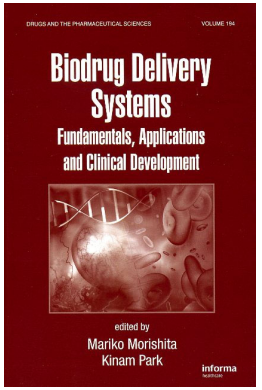
Scale-up production

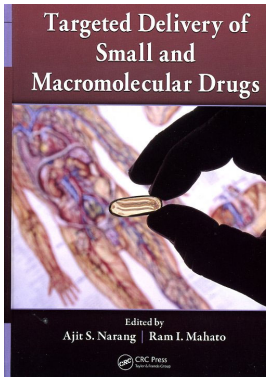
Stability

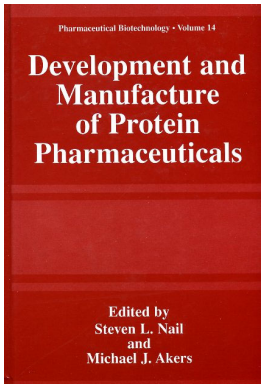


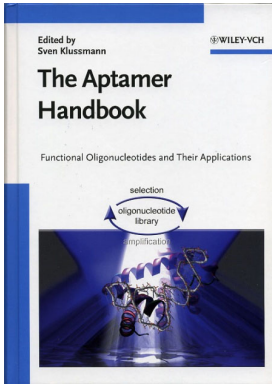


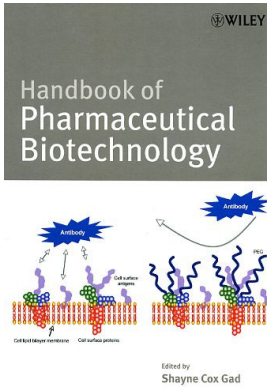










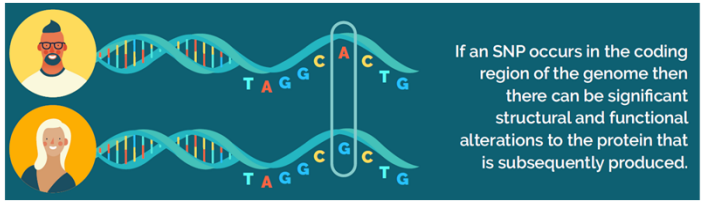


Drug Delivery: Future

Precision Medicine

Pharmacogenetics

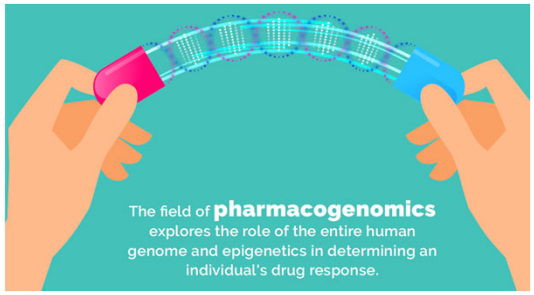
The study of genetic factors (heredity) that influence response to drugs and the predisposition to develop adverse effects.
The correlation of the DNA sequence of genes to a drug response.



Pharmacogenomics

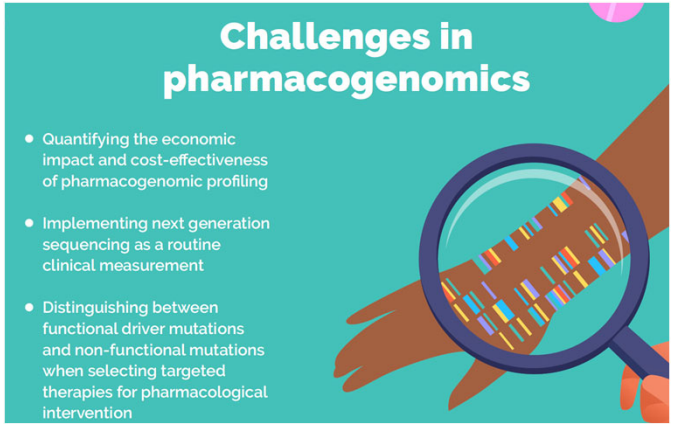
The implementation of large-scale genomic approaches to this question.
The study of the pattern of expression of genes involved in a drug response in a defined environment.

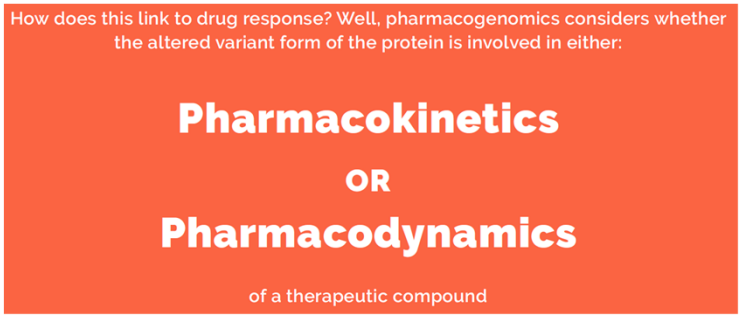
Pirmohamed 2001, Pharmacogenetics and pharmacogenomics

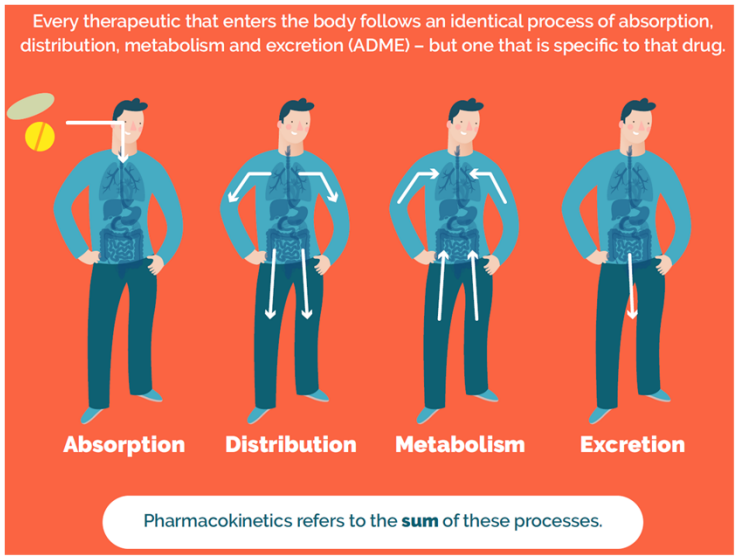


Precision Medicine

"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).

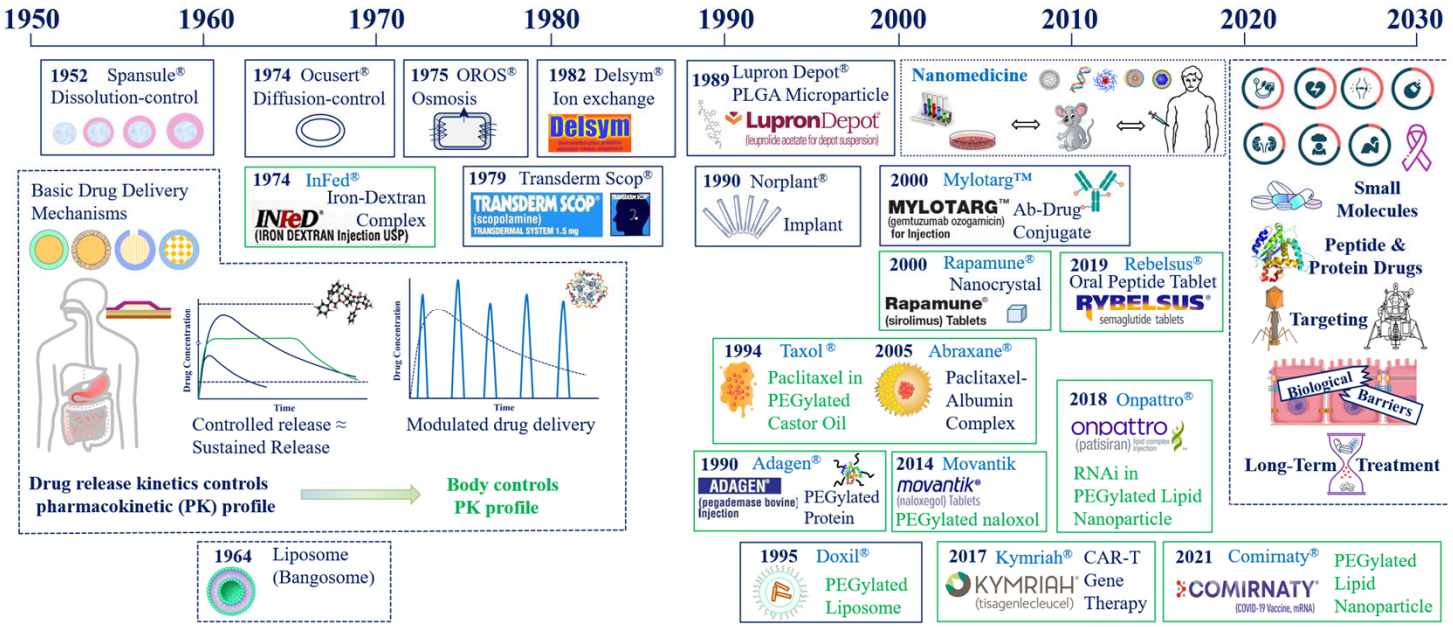






Technology Nwtworks 2020, Pharmacogenomics - Infographic

Challenges for Future Drug Delivery Systems



Oral / Transdermal delivery systems

Drug release kinetics by the system
In vitro release kinetics

⇩

In Vivo PK

Physicochemical properties
Engineering problems

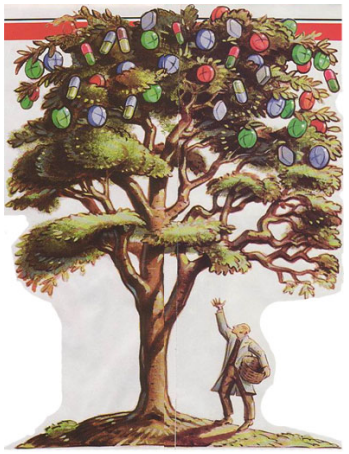
Injectable depot, Modulated, Nanomedicine

Drug release kinetics by the system
In vitro release kinetics

⇩

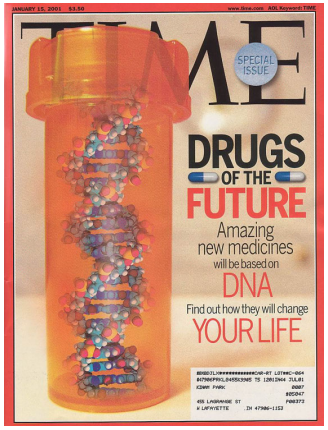
In Vivo PK

Physicochemical properties
Biological problems



Businessweek. May 6, 2002

Pfizer and Nektar's Exubera insulin inhaler (12 inches), 2006

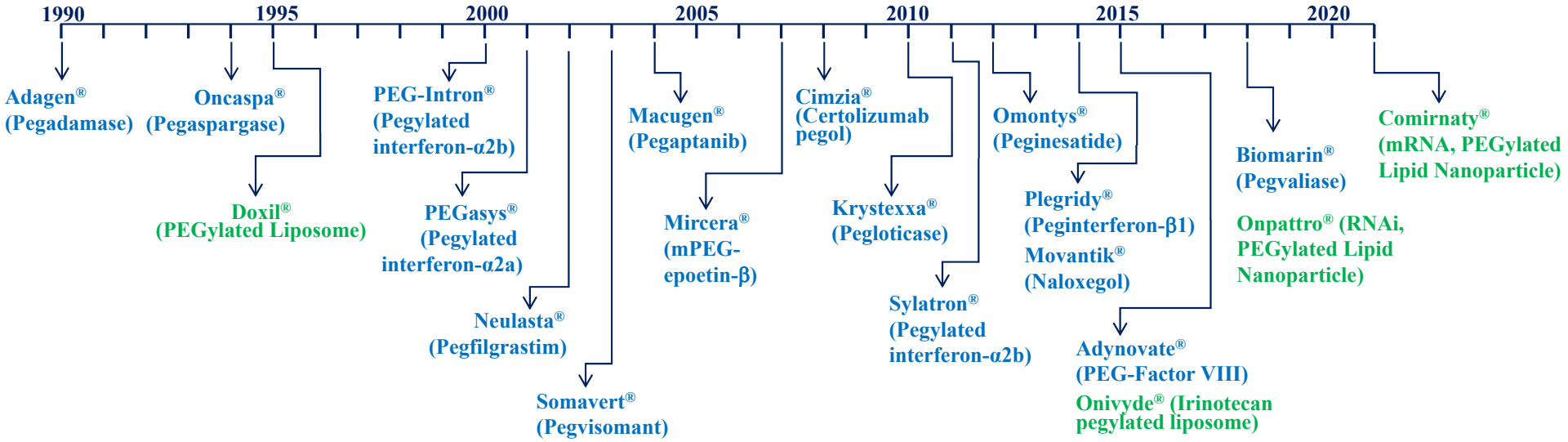


TIME. January 15, 2001

Challenging Drug Delivery Technologies

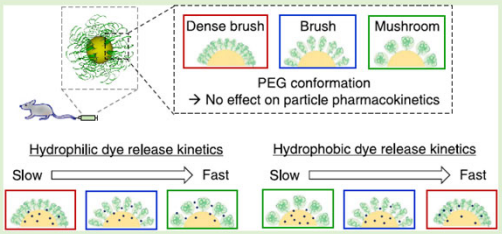
Delivery Technology	Formulation Barriers	Biological Barriers
Poorly water-soluble drug delivery	• New excipients for increasing drug solubility	• Non-toxic to the body • No drug precipitation in the blood
Peptide/protein/ nucleic acid delivery	• Control of drug release kinetics • Control of drug loading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

PEGylated Protein Drugs



PEG in Drug Delivery

ABSTRACT: In cancer chemotherapy, core-cross-linked particles (CCPs) are a promising drug carrier due to their high structural stability in an *in vivo* environment, resulting in improved tumor delivery. A biocompatible polymer of polyethylene glycol (PEG) is often utilized to coat the surface of CCPs to avoid nonspecific adsorption of proteins *in vivo*. The PEG density and conformation on the particle surface are important structural factors that determine the *in vivo* fate of such PEGylated nanoparticles, including their pharmacokinetics and pharmacodynamics. However, contrary to expectations, we found no significant differences in the *in vivo* pharmacokinetics and pharmacodynamics of the PEGylated CCPs with the different PEG densities including mushroom, brush, and dense brush conformations. On the contrary, the *in vivo* release kinetics of hydrophilic and hydrophobic model drugs from the PEGylated CCPs was strongly dependent on the PEG conformation and the drug polarity. This may be related to the water-swelling degree in the particle PEG layer, which promotes and inhibits the diffusion of hydrophilic and hydrophobic drugs, respectively, from the particle core to the water phase. Our results provide guidelines for the design of cancer-targeting nanomedicine based on PEGylated CCPs.



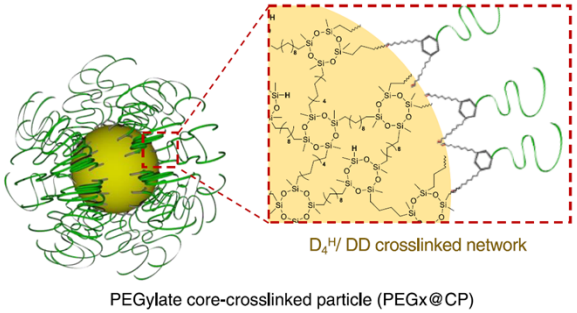


Figure 1. Schematic illustration of a PEGylated core-cross-linked particle (PEGx@CP) comprising a D4 H/DD cross-linked network core.

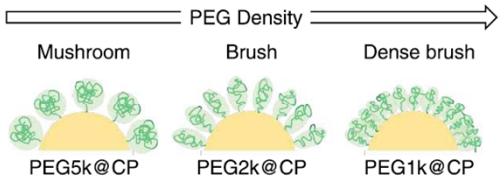


Figure 4. Schematic illustration of PEG conformations on **PEGx@CPs**: mushroom, brush, and dense brush.

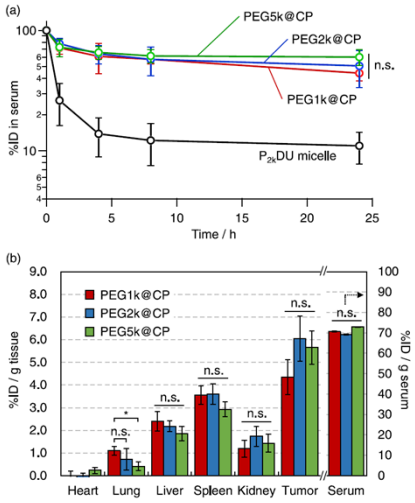


Figure 5. (a) *In vivo* pharmacokinetics of **PEGx@CP^{Cy5}s** (red, **PEG1k@CP^{Cy5}**; blue, **PEG2k@CP^{Cy5}**; green, **PEG5k@CP^{Cy5}**) and the **P$_{2k}$DU^{NBD}** micelle (black) after intravenous (IV) administration into mice at 1.0 quadrillion nanoparticles dosage. (b) Biodistribution of **PEGx@CP^{Cy5}s** (red, **PEG1k@CP^{Cy5}**; blue, **PEG2k@CP^{Cy5}**; green, **PEG5k@CP^{Cy5}**) 24 h after IV administration into mice. All data are represented as the mean ± standard deviation (n = 5). n.s., not significant. *P < 0.05 (one-way ANOVA with Tukey's multiple comparison test).

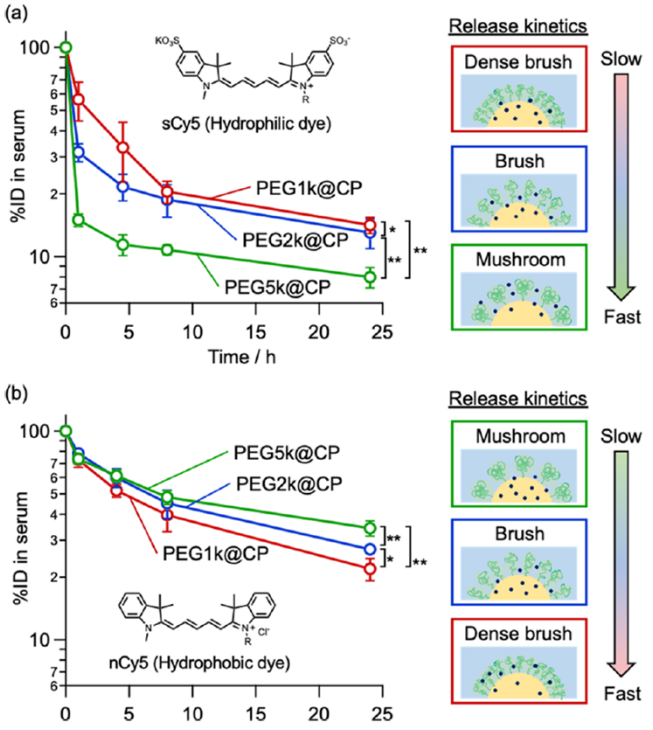
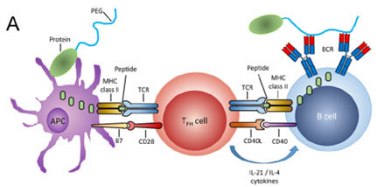
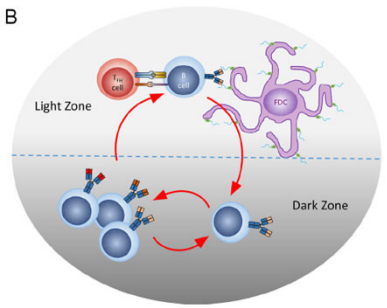


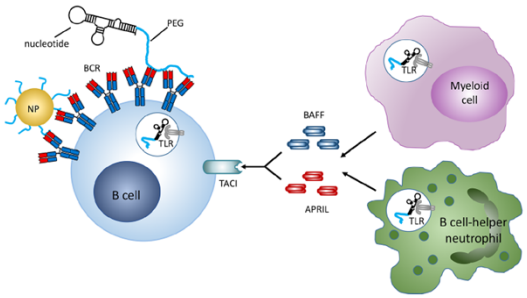
Figure 6. *In vivo* drug release kinetics of (a) sCy5 and (b) nCy5 included in **PEGx@CPs** (red, **PEG1k@CP**; blue, **PEG2k@CP**; green, **PEG5k@CP**) after intravenous administration into mice at a 1.0 quadrillion nanoparticles dosage. The chemical structures of sCy5 and nCy5 are displayed, where the R group is an alkyl chain with azide, and the details are displayed in Figure S17. All data are represented as the mean ± standard deviation (n = 5). n.s., not significant. *P < 0.05 and **P < 0.01 (one-way ANOVA with Tukey's multiple comparison test). The right images are schematic illustrations describing the relative release kinetics of each dye from **PEGx@CPs** with various PEG conformations.

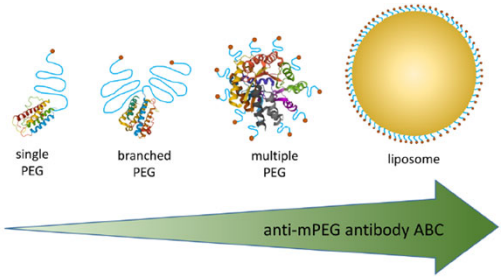
Kanamaru 2022, Impact of polyethylene glycol (PEG) conformations on the in vivo fate and drug release behavior of PEGylated core-cross-linked polymeric nanoparticles

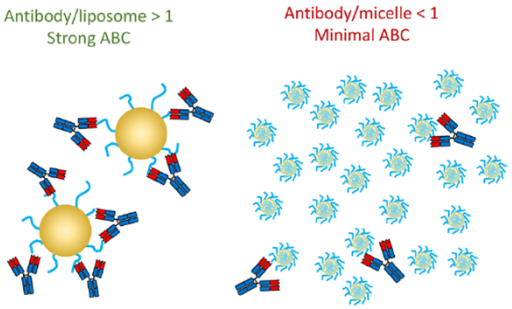
Antibodies against PEG

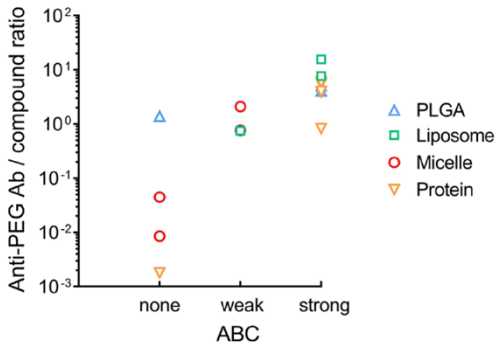












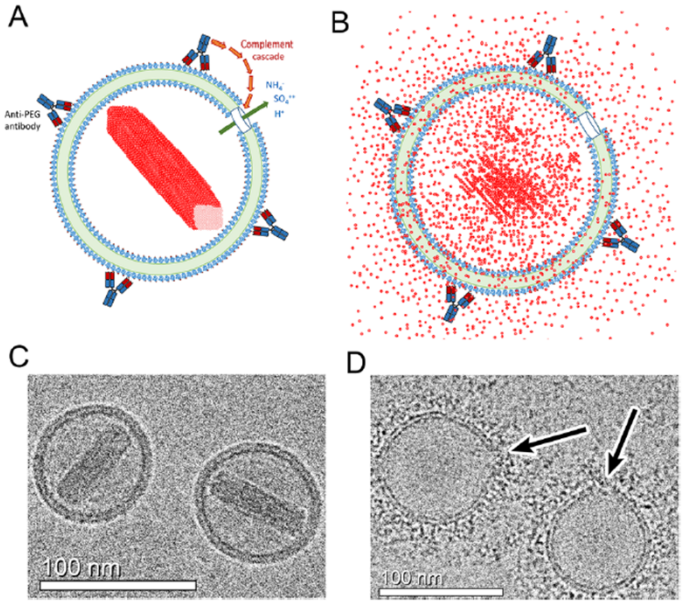


Figure 12. Anti-PEG antibodies can destabilize pegylated liposomal doxorubicin. (A) Anti-PEG antibodies that bind to PEGylated liposomal doxorubicin (PLD) can activate complement and cause formation of a membrane attack complex (which forms a pore) in the liposomal membrane, breaking the internal salt 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

In Vitro 3D Models Mimicking Human Physiology

Hemichannel model of breast cancer

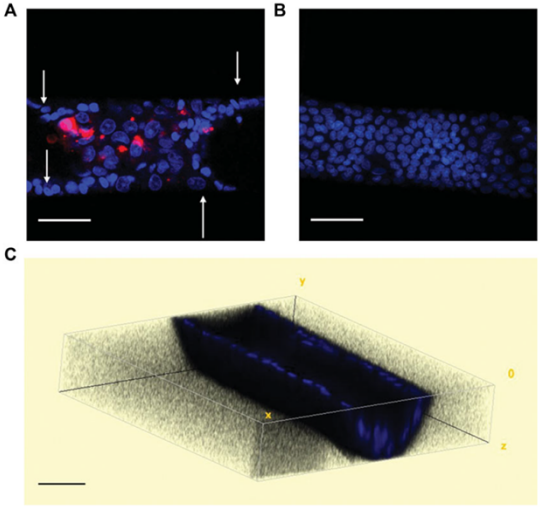


Figure 6 Coculture of non-neoplastic epithelial cells and cancer cells in the DOC. (A) Immunofluorescence image resulting from the staining of T4-2 tumors with dil prior to their seeding in the hemichannel. Non-neoplastic S1 cells were cultured on acrylic hemichannels covered with laminin 111 for 10 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

Tumor-Microenvironment-on-chip

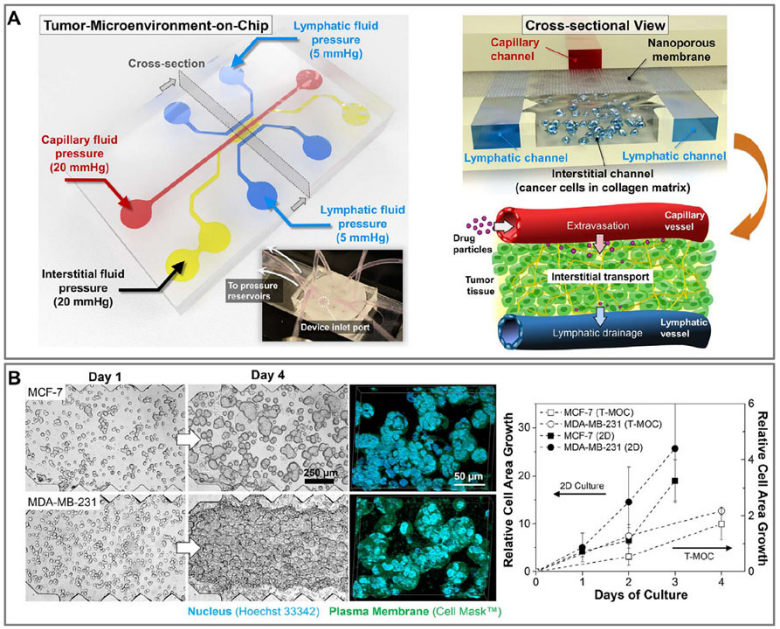
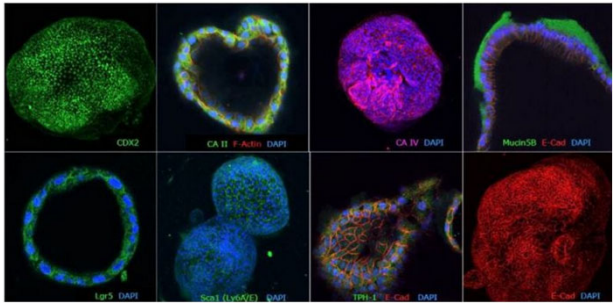


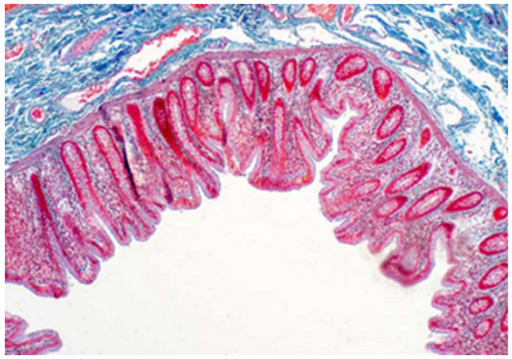
Fig. 1. Design and fabrication of T-MOC to simulate the drug transport at the TME. (A) Schematic of the fabricated T-MOC platform and its operating pressure conditions. Detailed 3D configuration of the device is illustrated in cross-sectional view – top layer with capillary channel, nanoporous membrane, 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.

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

3D Mini-Guts



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.



Human large intestine tissue under a microscope.

https://www.the-scientist.com/research-products-blog/mini-guts-to-the-rescue-introducing-3-d-organoid-cell-cultures-69623?utm_campaign=TS_3RD%20PARTY_2022&utm_medium=email&_hsmi=201625241&_hsenc=p2ANqtz-9onuHX_7Vbam5KXmXyGPDg6Qm-yjx4WVswqzHZsveztQXPnqVsPfozxvtiD9qUh5KfBS4G1U9rIJKyAeEwxD2F3z1cWw&utm_content=201597738&utm_source=hs_email