武汉大学本科课程之

药 学 导 论

—药剂学—

本节主讲：台万一

武汉大学药学院

内容概要

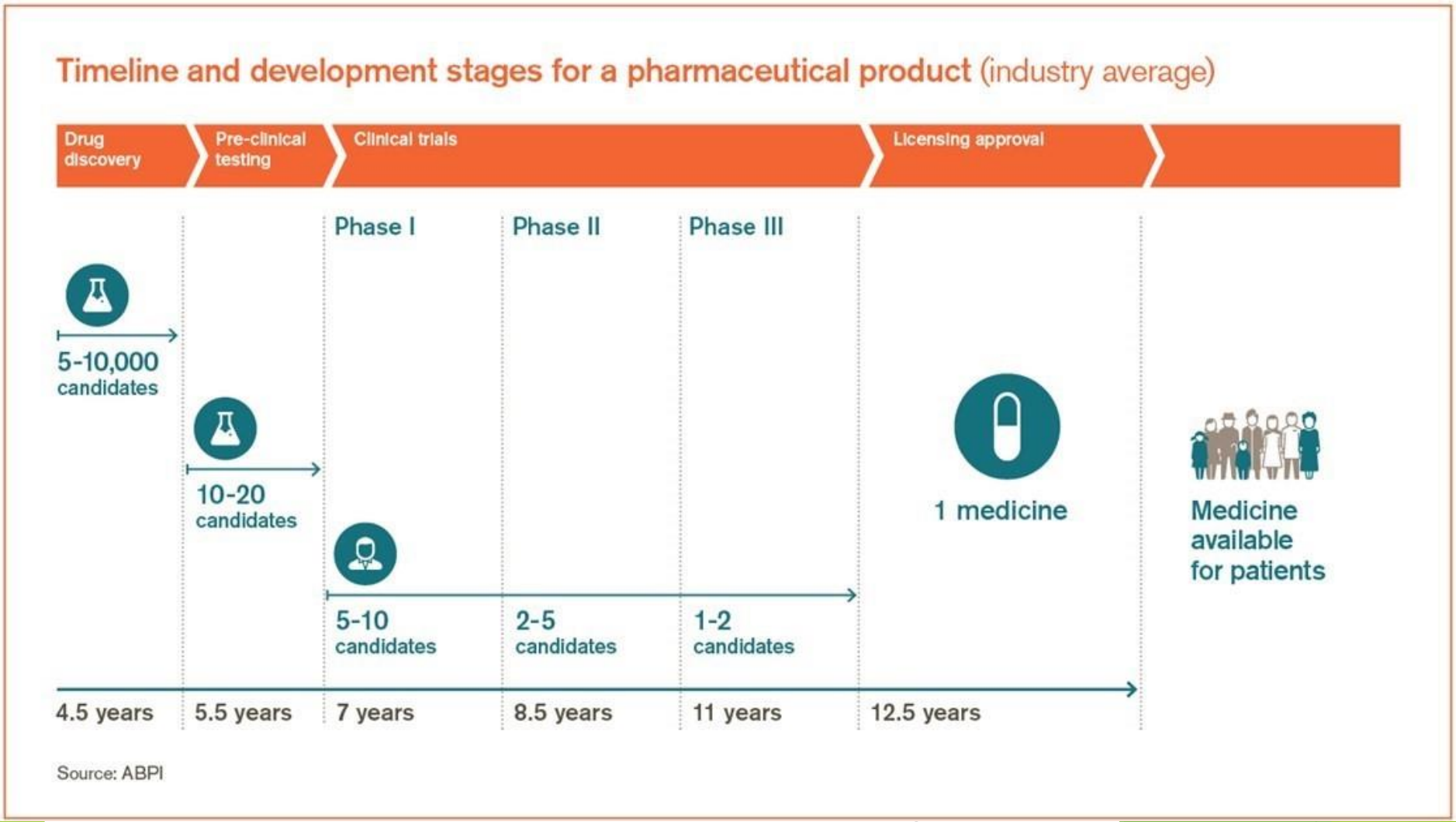
- 药剂学
  - 药剂学简介
  - 药剂学发展历史
  - 经典剂型介绍
  - 药剂学发现新趋势

第一节：新药研发与药剂学

新药研发难度大

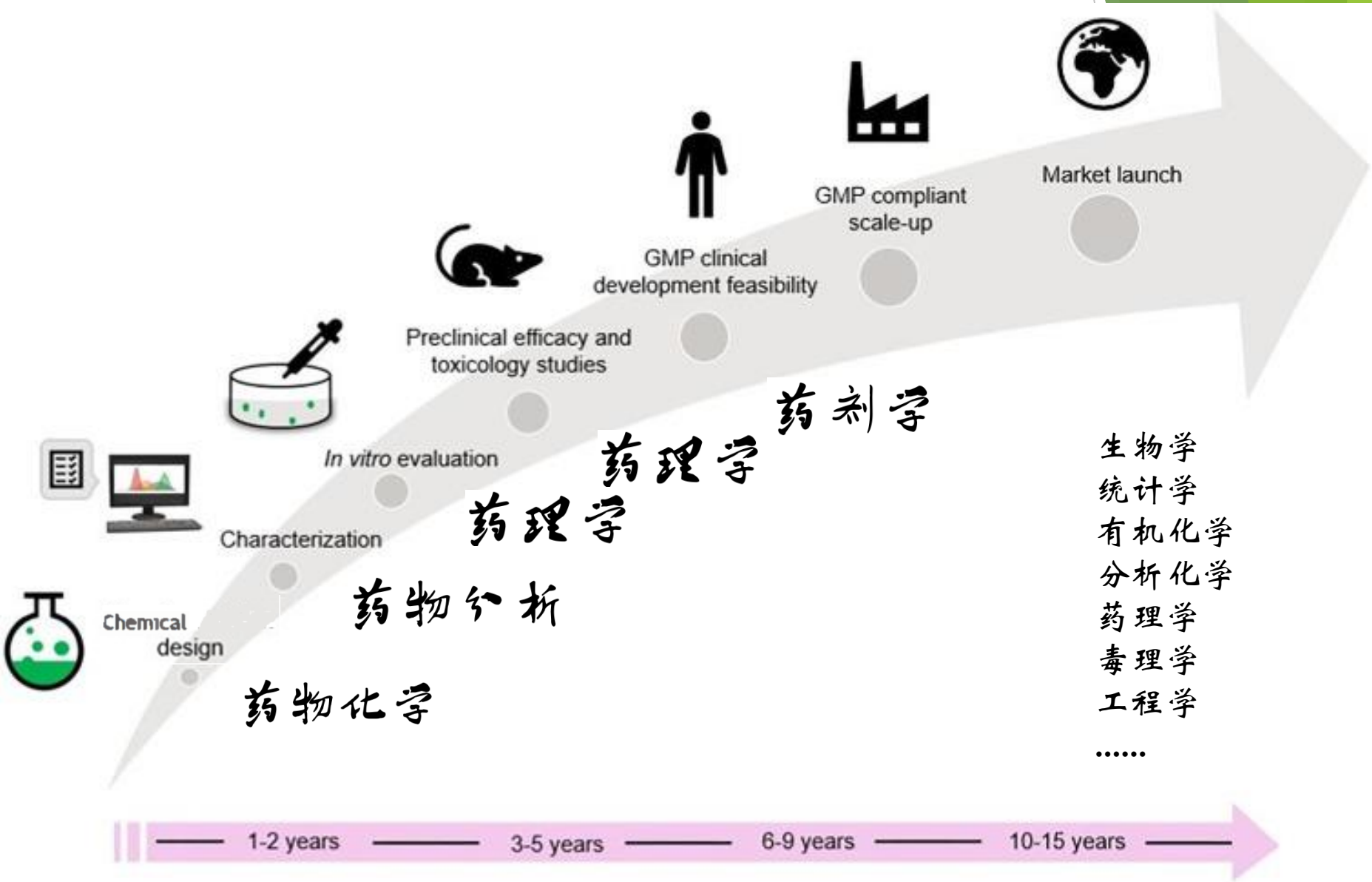

成功率3%，药物研发的冒险历程
FREES
长周期、高投入、高风险：药物研发的三个「10」
耗时10年以上
成本10多亿美金
10亿美金销售额

新药研发流程长



https://www.gsk.com/

新药研发涉及学科多


Market launch
GMP compliant scale-up
GMP clinical development feasibility
Preclinical efficacy and toxicology studies
In vitro evaluation
Characterization
Chemical design
药剂学
药理学
药理学
药物分析
药物化学
生物学
统计学
有机化学
分析化学
药理学
毒理学
工程学
.....
1-2 years
3-5 years
6-9 years
10-15 years

监管严、后果严重、专利期短

GxP

GMP GOOD MANUFACTURING PRACTICE

GLP GOOD LABORATORY PRACTICE

GDP GOOD DOCUMENTATION PRACTICE

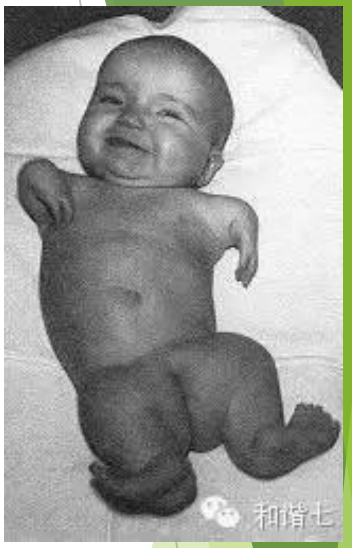
GCP GOOD CLINICAL PRACTICE

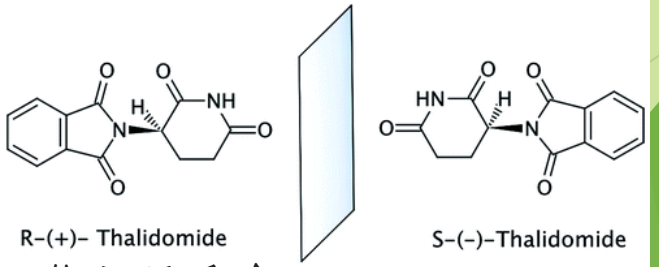
GSP Drug supply

GPP Drug Retail

GUP Drug using

欧洲‘反应停’事件





抗妊娠反应

致畸性

沙利度胺（Thalidomide）又名反应停

全球化学分子实体

是真正意义上的新药，数量非常少

新药研发的Me策略

新药研发很费钱、很难，所以有很多“投机”创新

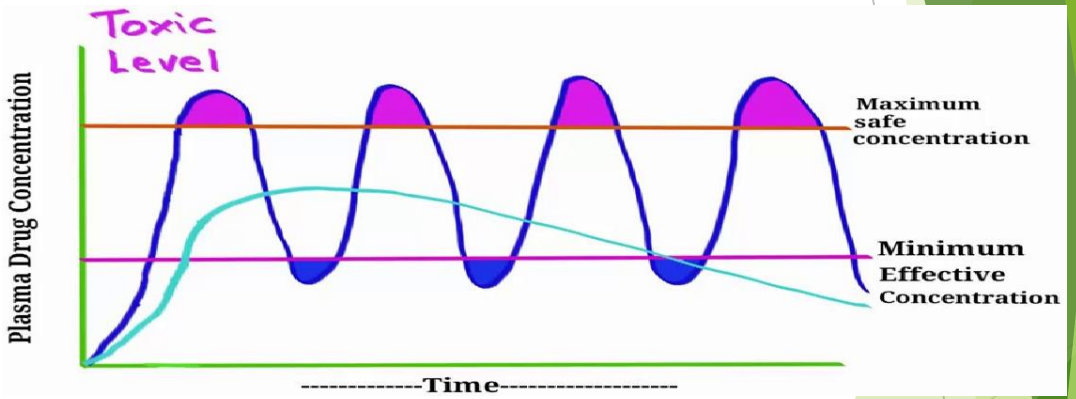
Me too，me better，fast follower

药剂学——“盘活存量、用好增量”

李克强总理强调金融资源配置要“盘活存量、用好增量”！

药物分子的增量和存量都很少，药剂学就是研究怎么最好的用好这些药物分子资源。

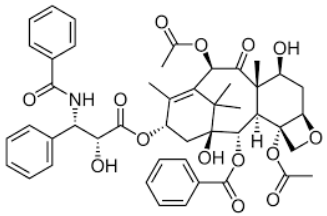
例一：提高安全性和疗效



例二：化腐朽为神奇


红豆杉


紫衫树皮提取紫杉醇



紫杉醇
水不溶

第二节：药剂学简介

药剂学与药学各学科

药剂学（Pharmaceutical science）是一门研究药物制剂剂型的处方设计、生产工艺、合理应用以及药物制剂剂型和药物的吸收、分布、代谢及排泄关系的综合技术科学。

— 摘自维基百科

药物代谢动力学

临床药学

生药学

制药工程与机械

药物信息学

药剂在新药研发中的作用

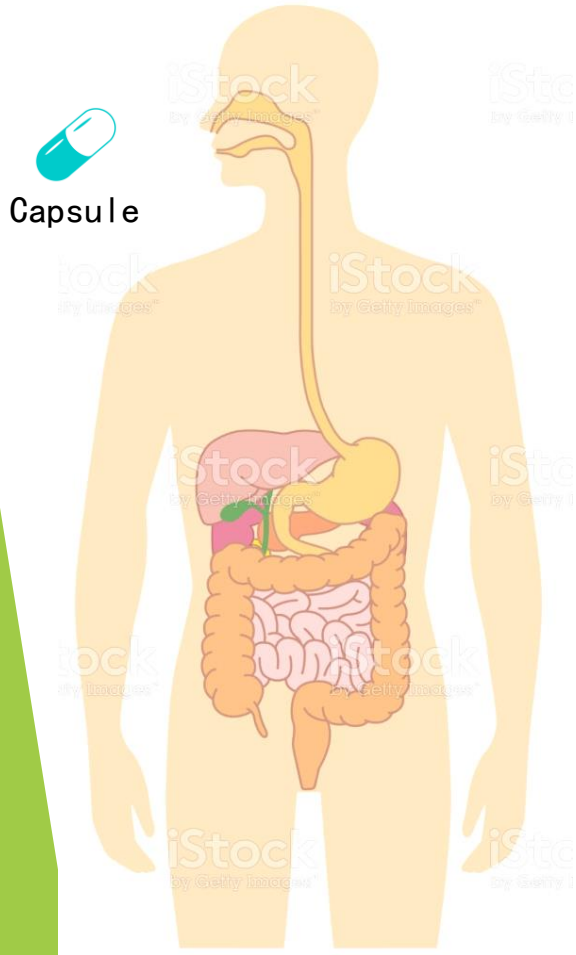
药剂作用：

- 准确剂量 Dosage
- 提高药物生物利用度 Bioavailability
- 降低毒副作用 Side effect
- 依从性 patients'compliance

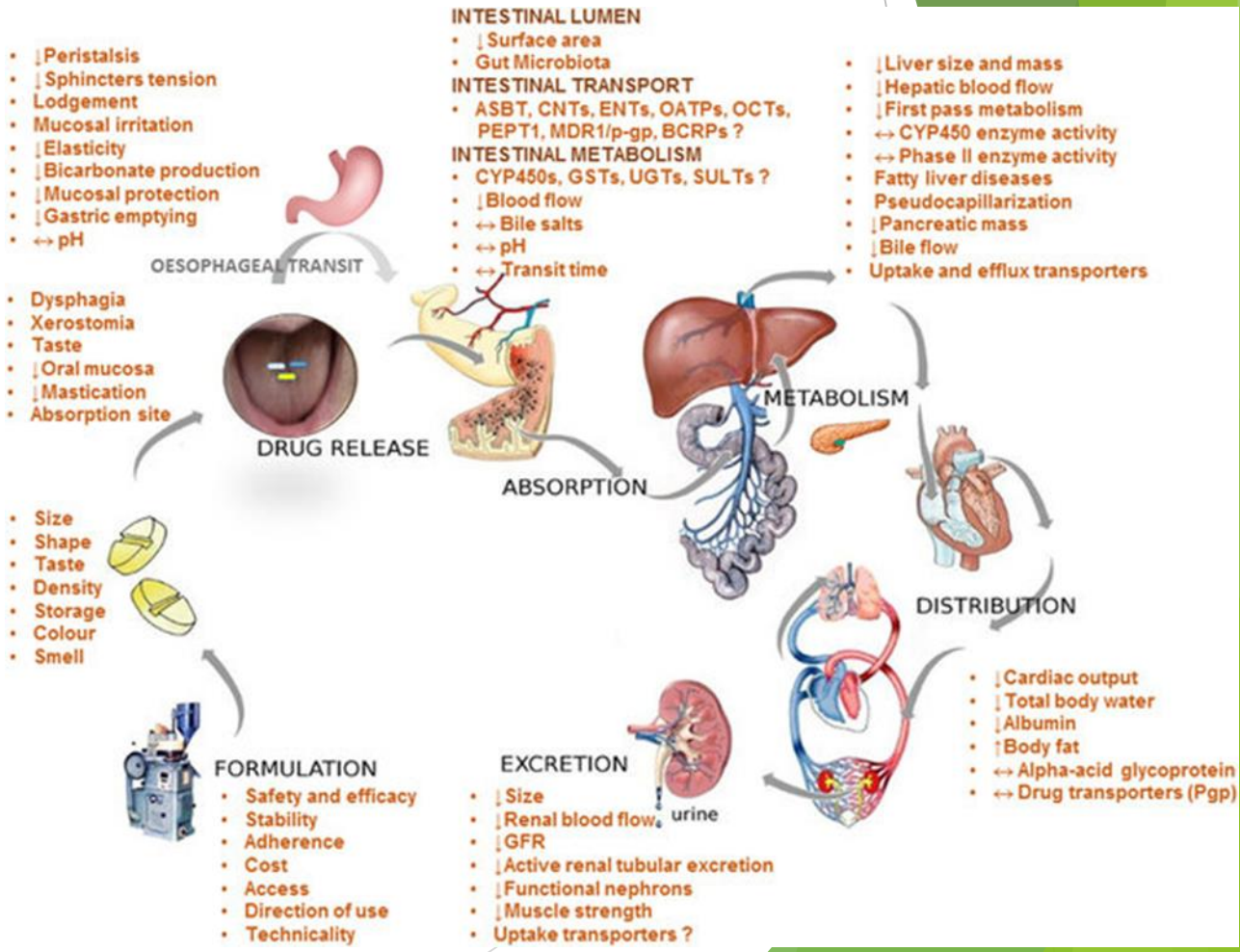
药剂学研究内容

研究的问题：怎样将活性药物成分递送到发挥疗效的位置

研究的难题：复杂多变的体内环境和递送障碍

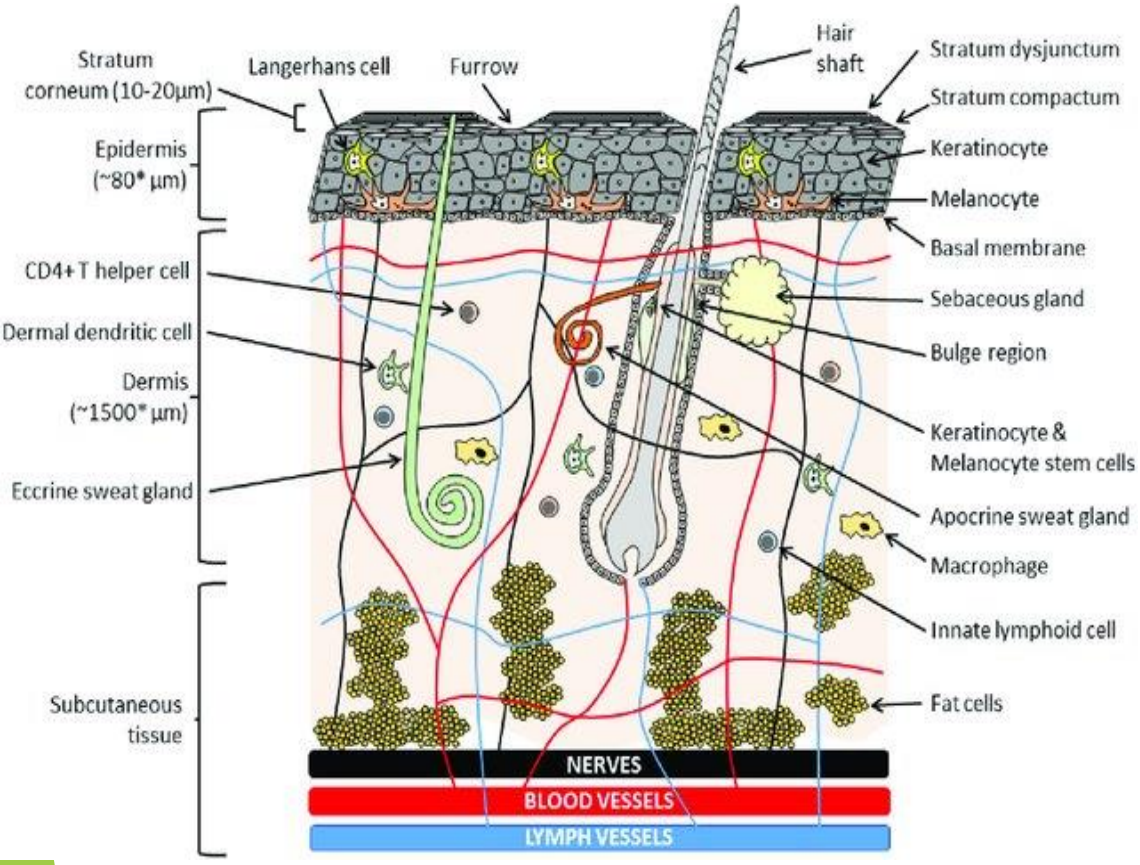


口服制剂与消化道系统

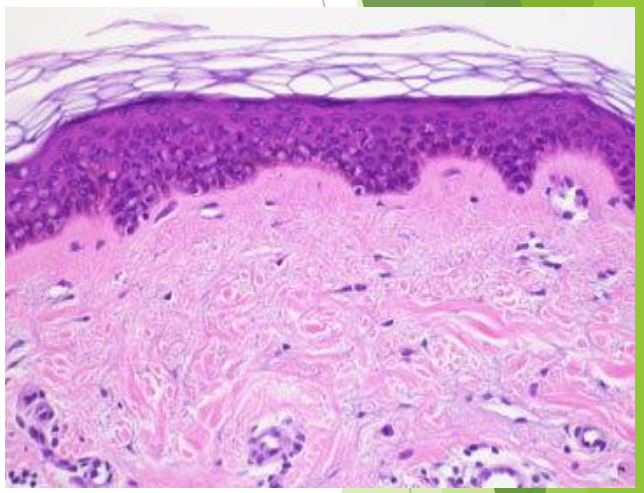


药剂学研究内容

递送障碍----以透皮递送为例



人体皮肤组织结构

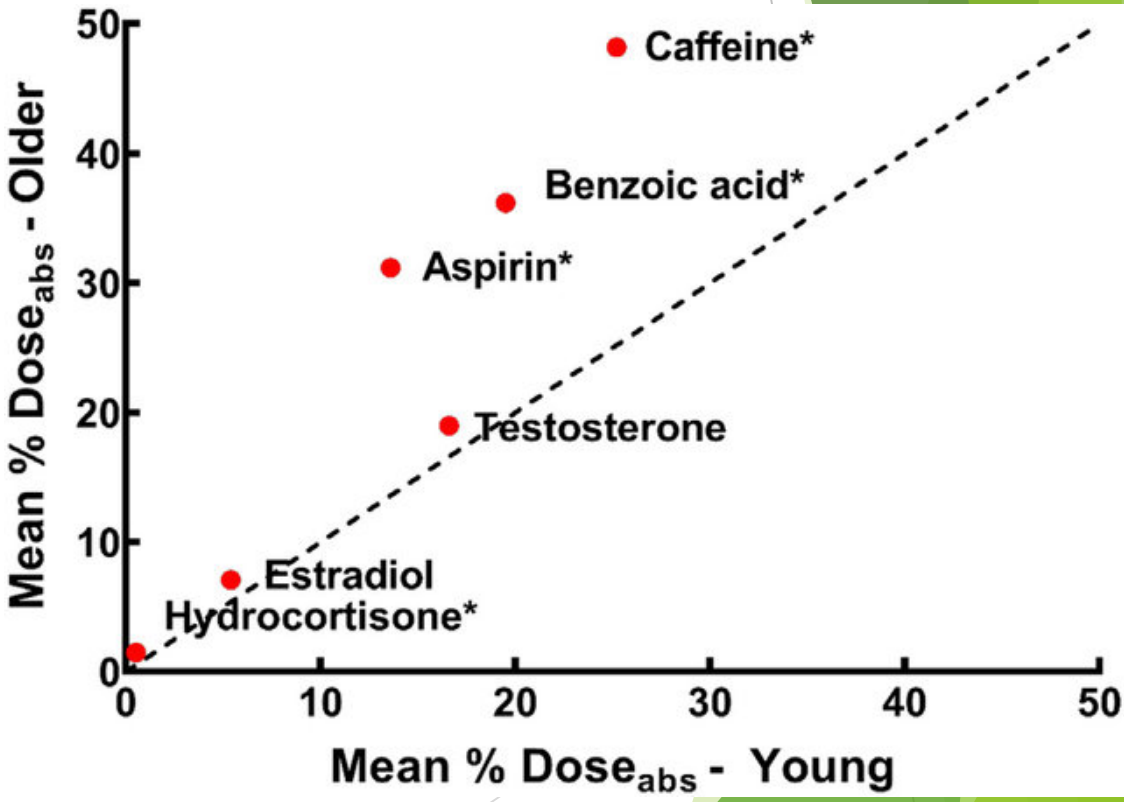


皮肤组织染色图

药剂学研究内容

递送障碍----以透皮递送为例

递送障碍会随着环境和个体发生变化



药物在不同年龄组病人透皮吸收的差别

Adv Drug Deliv Rev . 2018 Oct;135:3-38

药剂学研究内容

药剂学手段

- 剂型辅助活性成分到达 —— 辅料配伍
- 给药途径
- 修饰活性药物成分 —— 前药
- 靶向

药剂学研究内容

剂型　通过药物活性成分与辅料组合，制备剂型，提高生物利用度、依从性等。

常用药用辅料

- 微晶纤维素
- 玉米淀粉
- 聚乙烯醇PVC
- 滑石粉
- 其它药用高分子材料

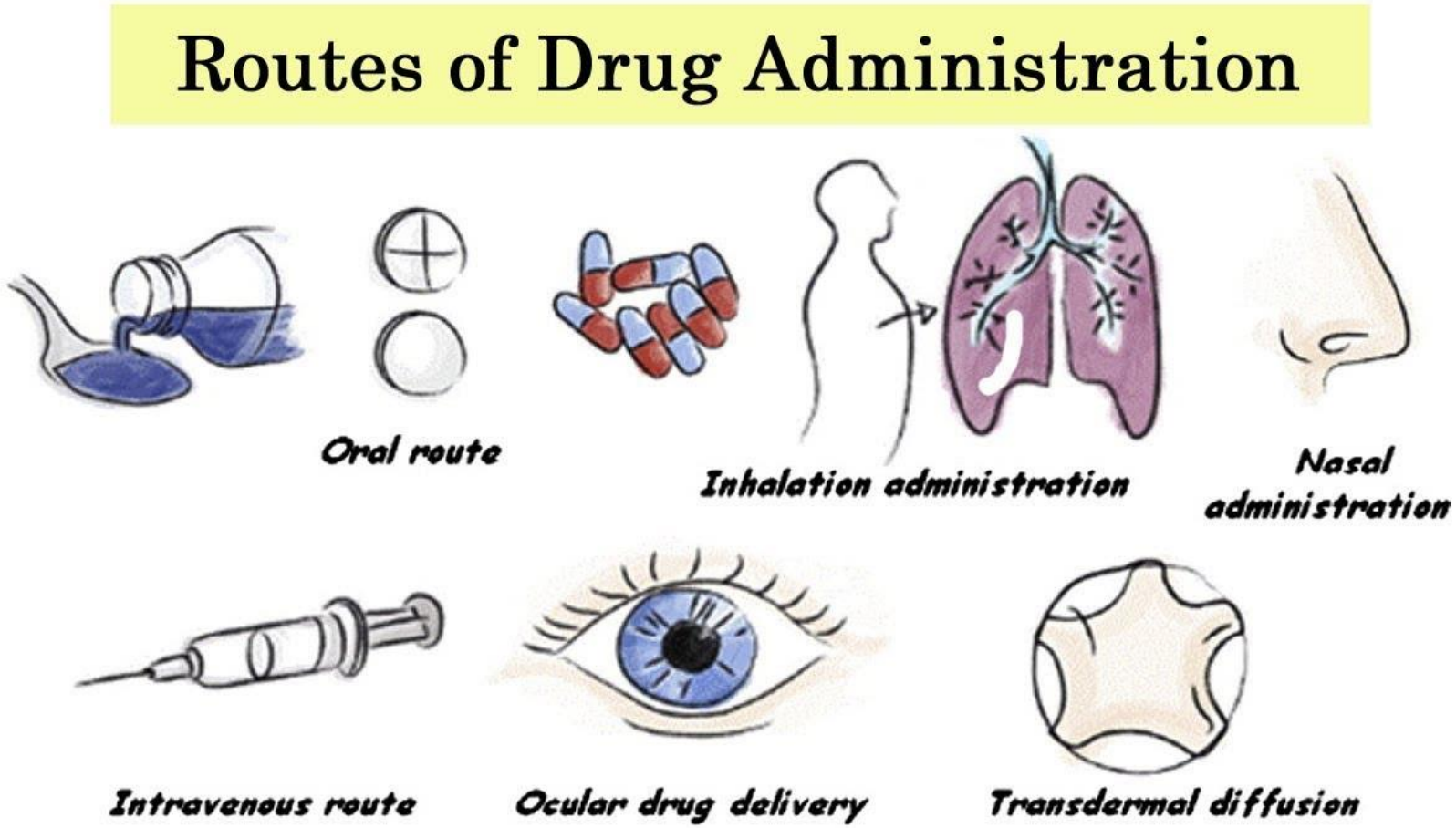
2010年版《中国药典》共收载辅料132个

2015年版《中国药典》共收载辅料品种270个

2020年版《中国药典》共收载辅料335个

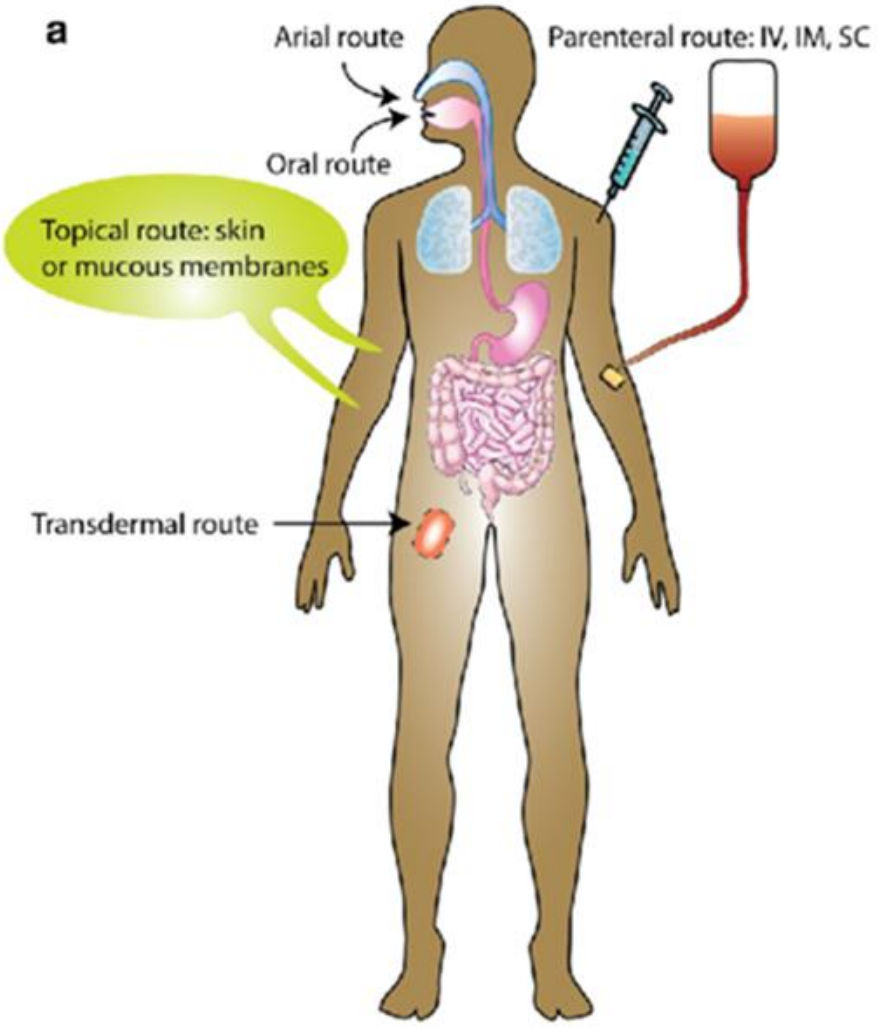
药剂学研究内容

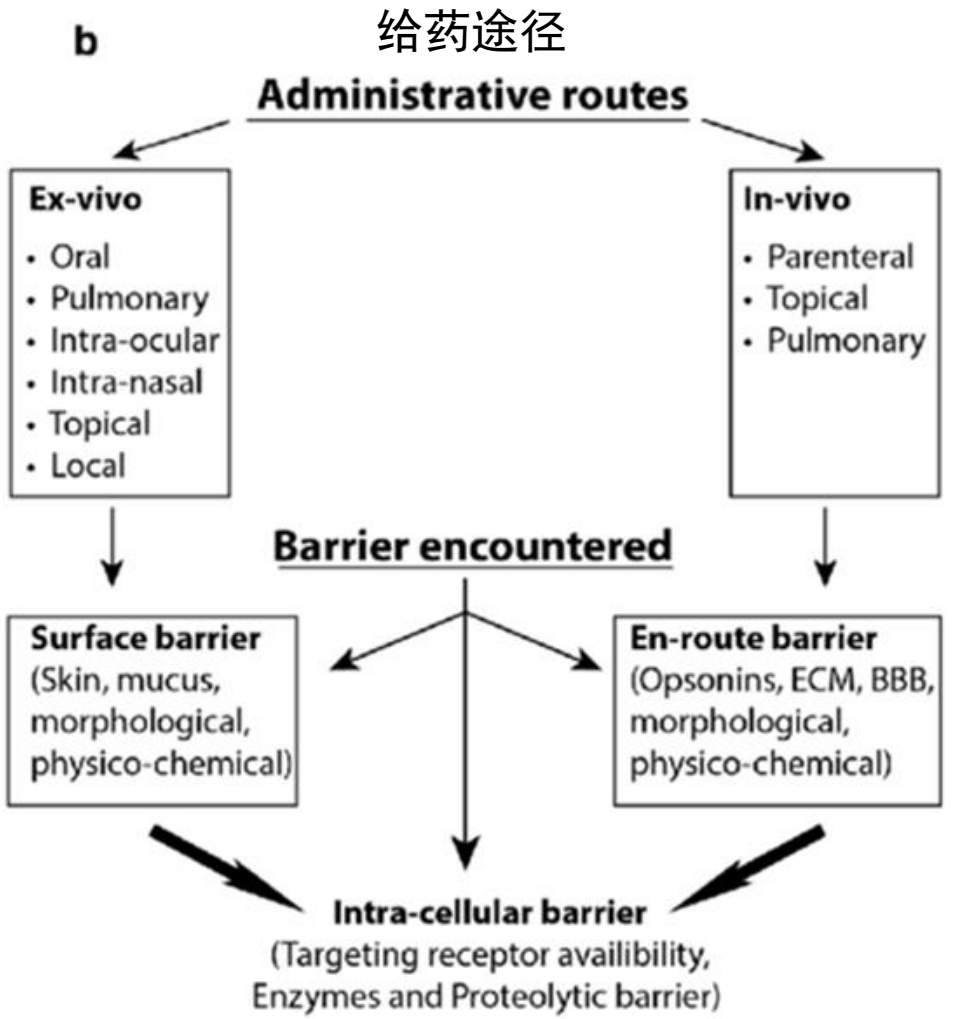
给药途径



药剂学研究内容

给药途径与递送障碍





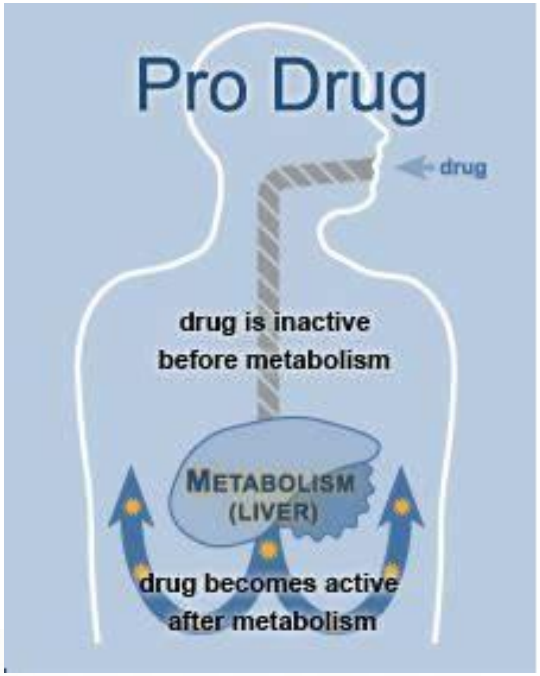
药剂学研究内容

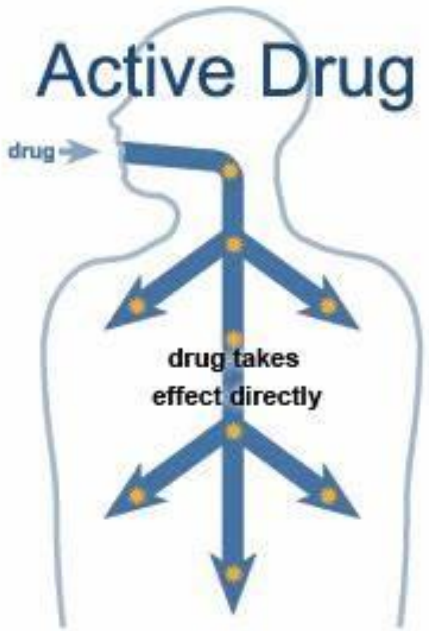
修饰活性药物成分

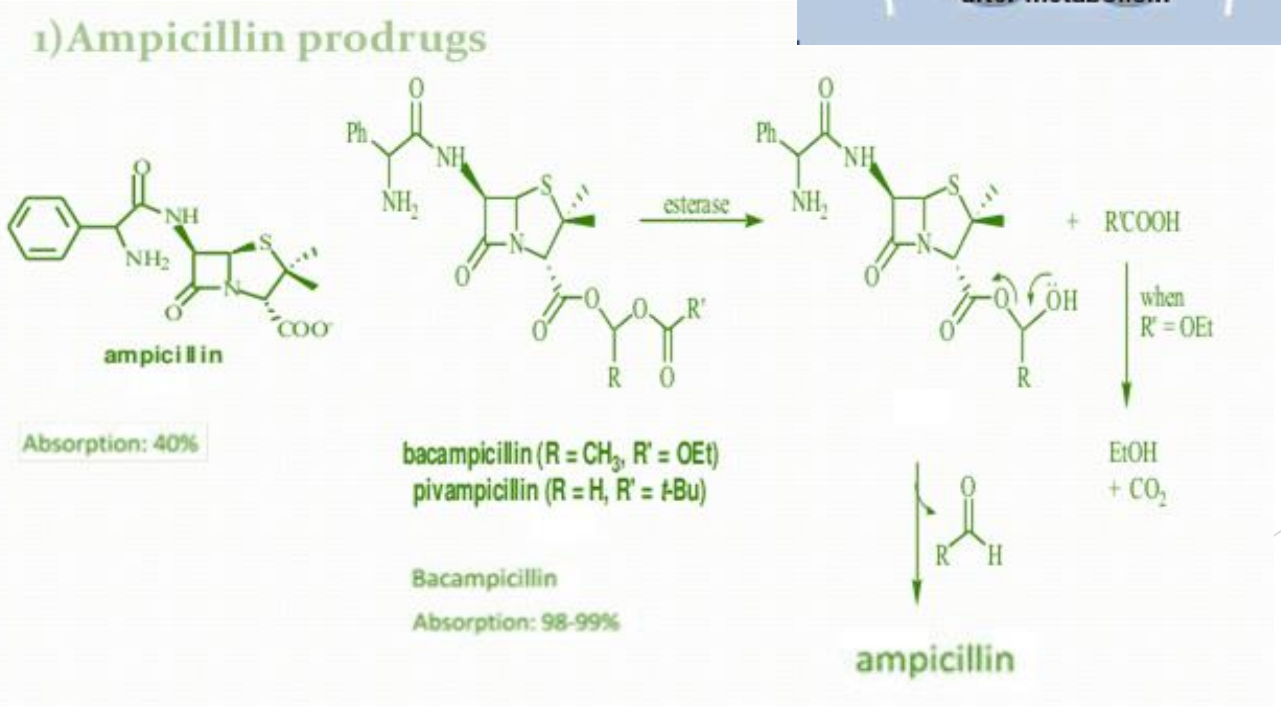
前药 （Prodrug）

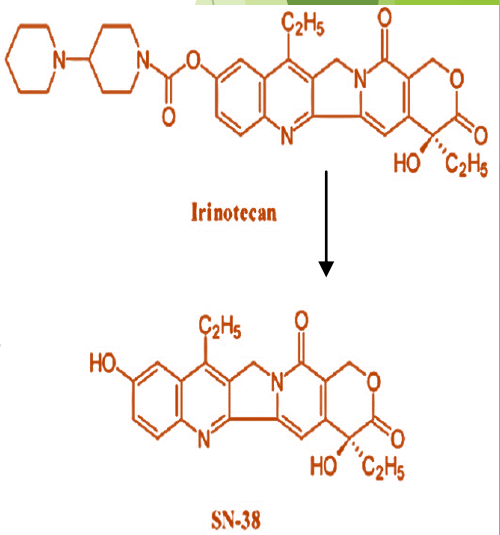
提高生物利用度，降低毒性

前药



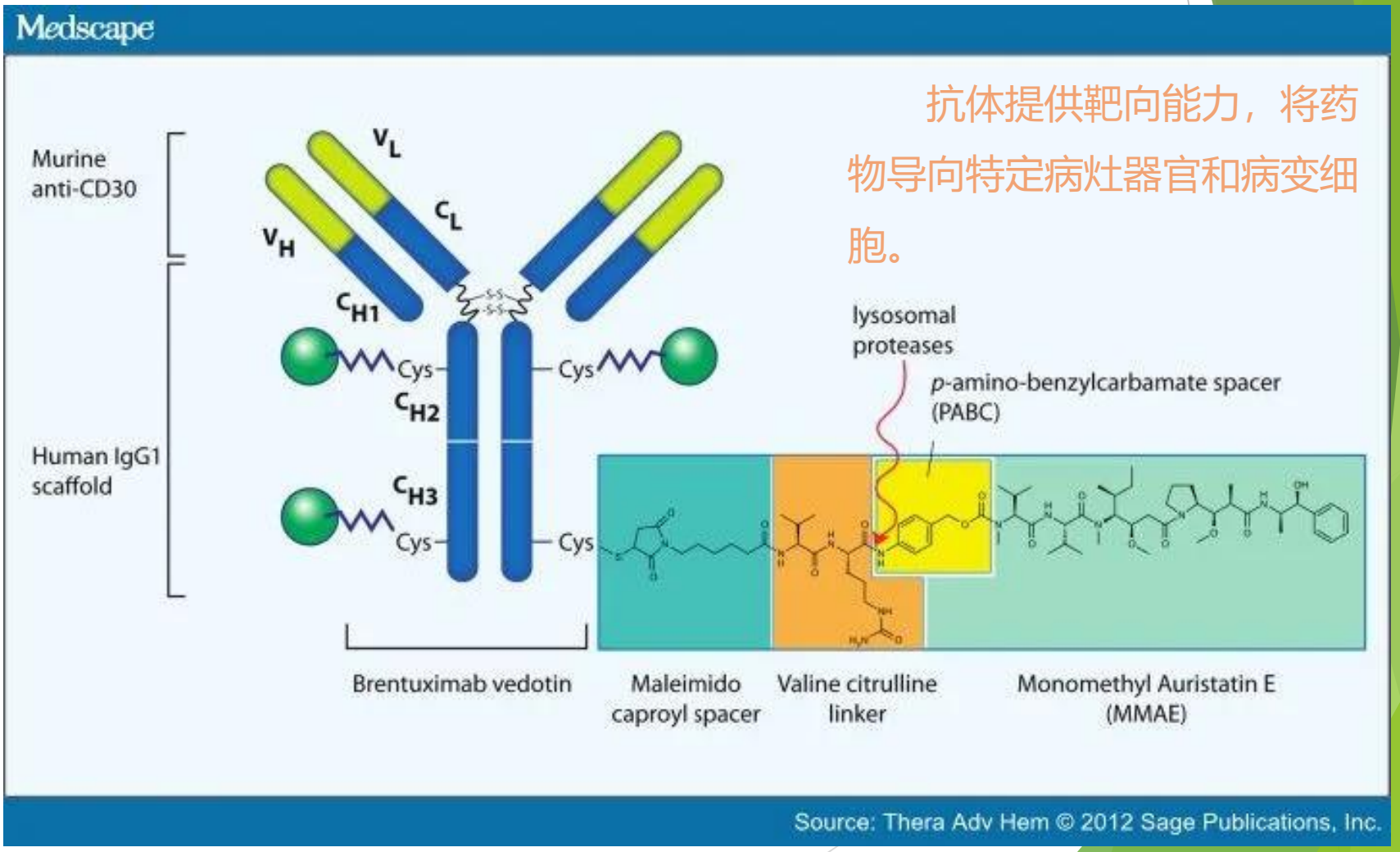




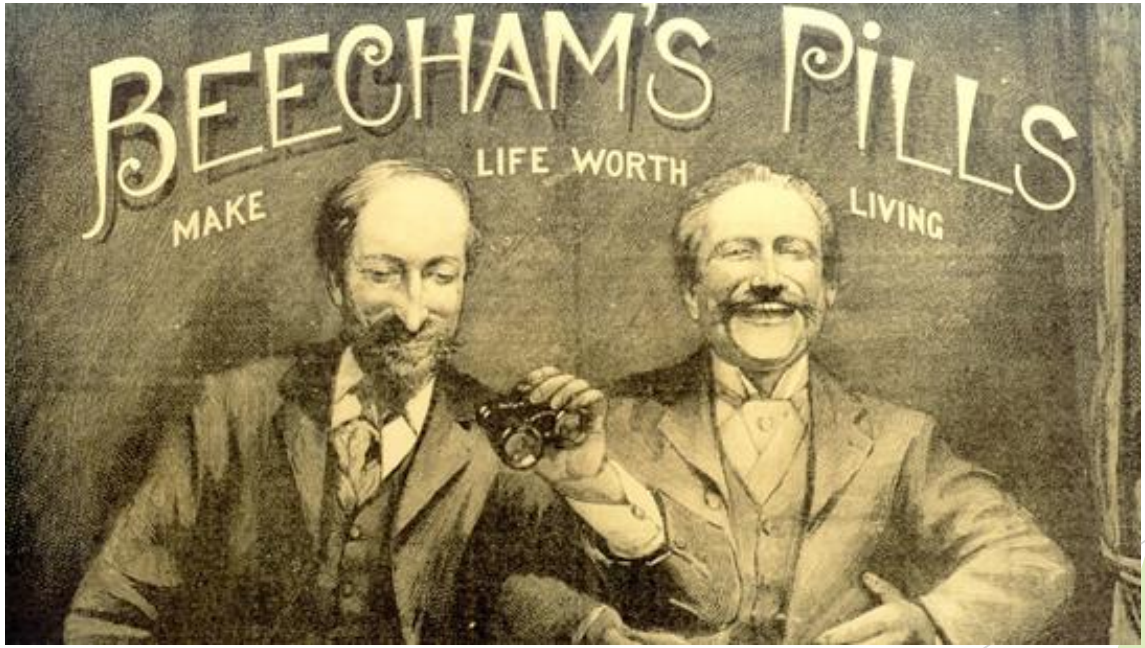


药剂学研究内容

靶向制剂　　提高靶向性，降低毒性



第三节：药剂学发展历史



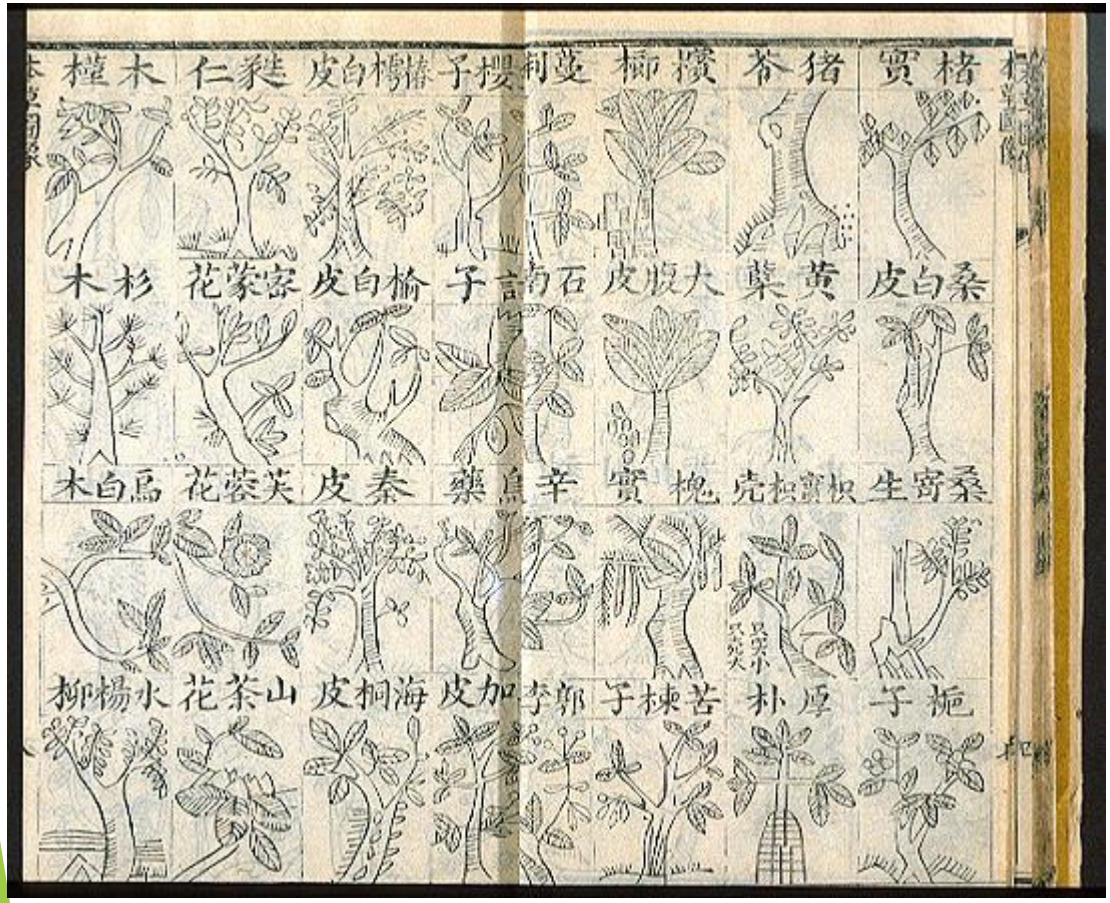
远古时代以液态药物为主

埃及纸草书描述大麻用途

- 携带不便
- 剂量不准
- 易变质

中医理论指导下的中药

以本草药物为主，具有中医理论指导优势



中国古代药剂剂型

酊剂

蜜丸

丹剂

黑膏药

制法简陋但初步具备现代药剂特质

中国古代透皮制剂-黑膏药

南宋李唐《村医图》

配方

- 植物药料
- 炼油
- 黄丹
- 麝香或冰片
- 膏药布

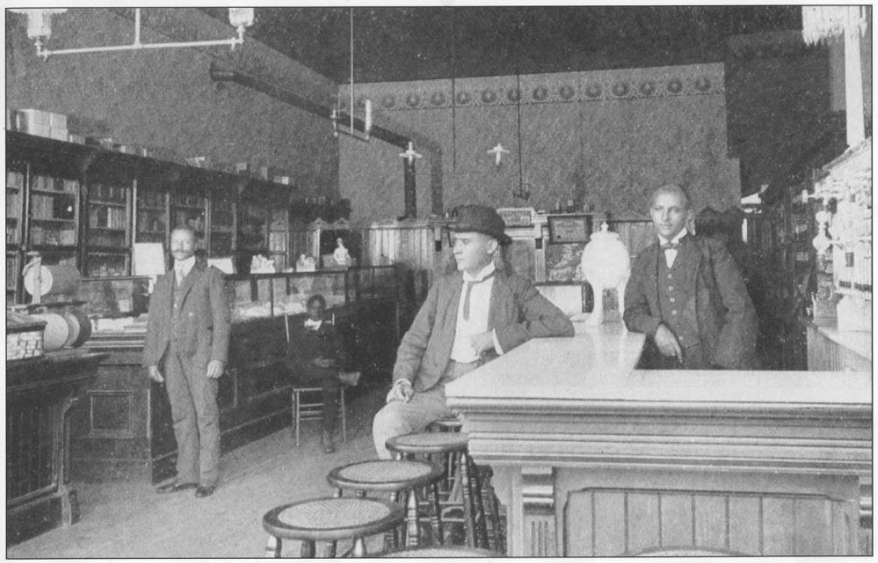
黑膏藥

- 下丹成膏：煉成之油(2)＋紅丹→化學反應產生脂肪酸鉛→氧化、聚合、增稠成膏狀。
- 【範例】
- 植物油500g＋紅丹150-210g；T＝300℃；不斷攪拌下加入紅丹。
- 去火毒：症狀－局部刺激性，輕者紅斑搔癢；重者則發泡潰瘍。
- 火毒生成原理：1.高溫下產生的『燥性』2.現代藥理－植物性油→高溫下之氧化聚合反應→低分子之分解產物→醛、酮、低級脂肪酸→ 溶於水而驅除火毒。
- 火毒去除法：水中浸泡，久置陰涼處。

Pharmacist

欧美在初期药物制剂以药剂师和药剂师店铺为主。

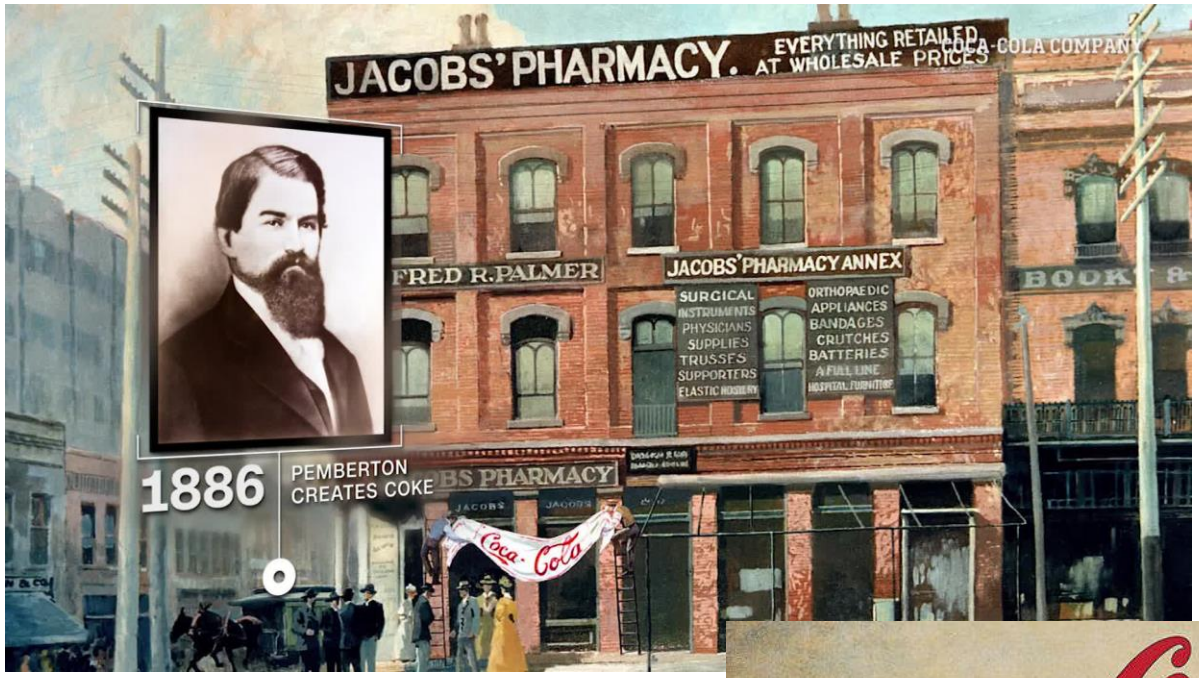
药剂师和药店以秘密配方为宣传点。



Interior of James and Allen Drug Company of Chattanooga, TN, c. 1900, a black-owned pharmacy featured in the book, Progress of a Race, *1902.*

18世纪欧美药剂师和药店

药剂师、药剂学、可口可乐



John Pemberton (美国亚特兰大)

coca-leaf extract

+

kola-nut extract

+

sugar syrup

制药公司初期以小作坊为主

Novartis 药厂 1914

Pill、Tablet、Capsule

In 1843, English inventor William Brockedon was granted a patent for a device capable of “shaping pills, lozenges and black lead by pressure in dies."

最原始的片剂是有面筋和药物混合压片组成，主要目前是为了精确药物定量

1860年喹啉压片机

Pill

Tablet

Capsule

现代片剂

大小与剂量

植入片可用针头注射

鱼肝油House pill

形状与颜色

Takeru Higuchi 现代物理药剂学之父

药物释放模型方程

Mathematical model for drug dissolution
Higuchi (Equation)

$$Q = [D(2A - C_S)C_S t]^{\frac{1}{2}}$$

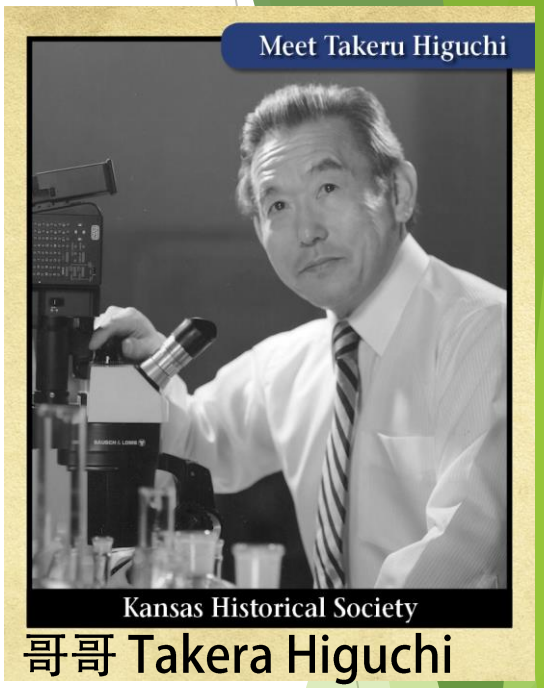
$$\frac{dQ}{dt} = \frac{1}{2}\left[\frac{D(2A - C_S)C_S}{t}\right]^{\frac{1}{2}}$$

A>>>>Cs

$$Q = [2ADC_S t]^{\frac{1}{2}}$$

$$\frac{dQ}{dt} = \left[\frac{ADC_S}{2t}\right]^{\frac{1}{2}}$$

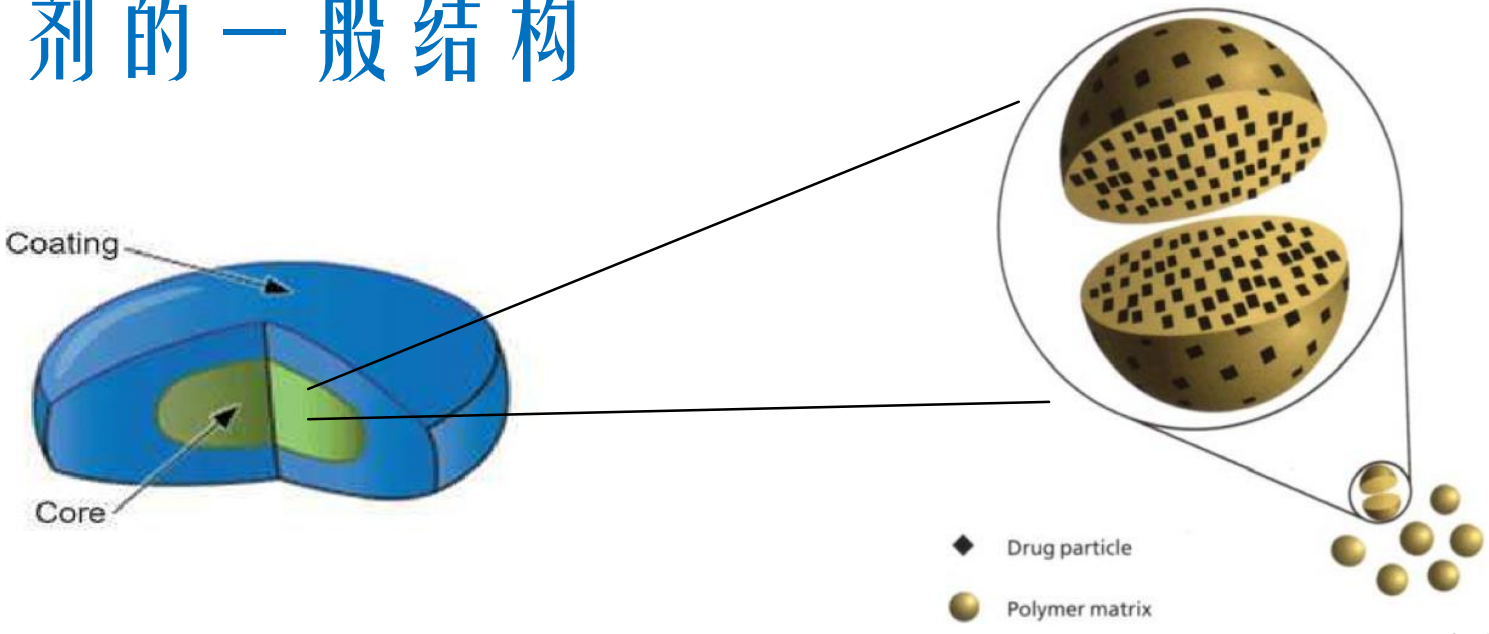
Q *amount of* the drug release in time t per unit area
dQ/dt the rate of drug released per unit area
A *is the total concentration* dissolved and undissolved, of drug in the matrix. OR
Total amount of drug in a unit volume of the matrix OR
The initial drug concentration
Cs is the solubility or saturation concentration of drug in the matrix
D, the diffusion coefficient of the drug in the matrix



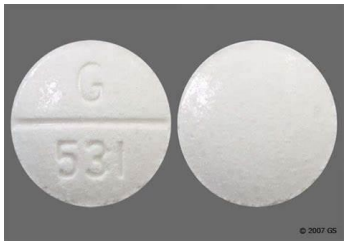
哥哥 Takera Higuchi


弟弟 William Higuchi

片剂的一般结构



素片

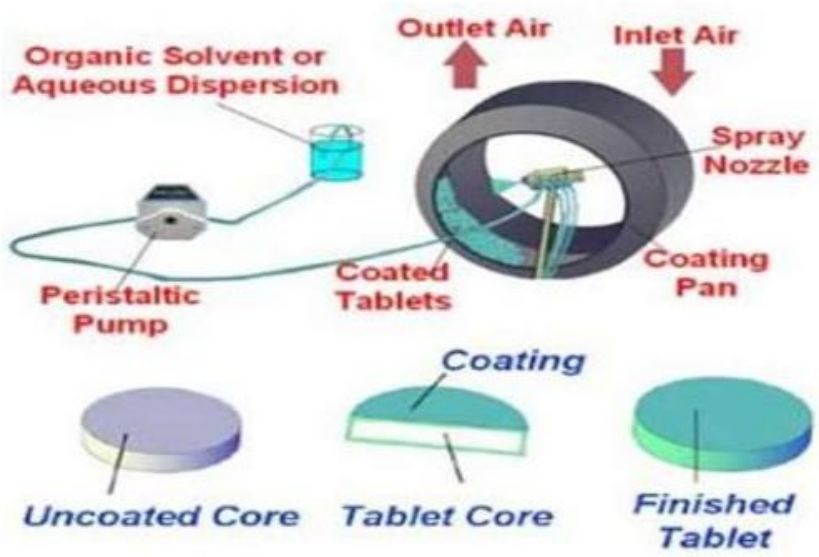


包衣片

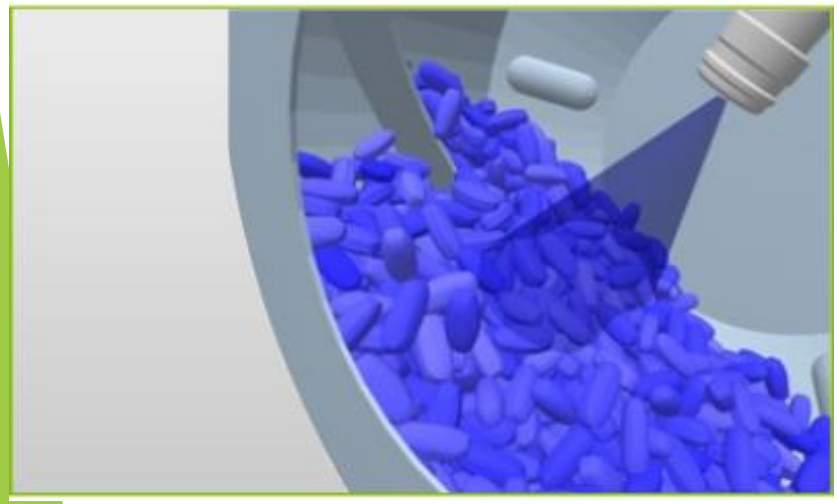
Tablet Coating

- Why coat tablets?
  - Taste and smell identity
  - Protect incompatibility
  - appearence
- Types of coatings
  - sugar coating
  - film coating
  - press coating (compression coating)

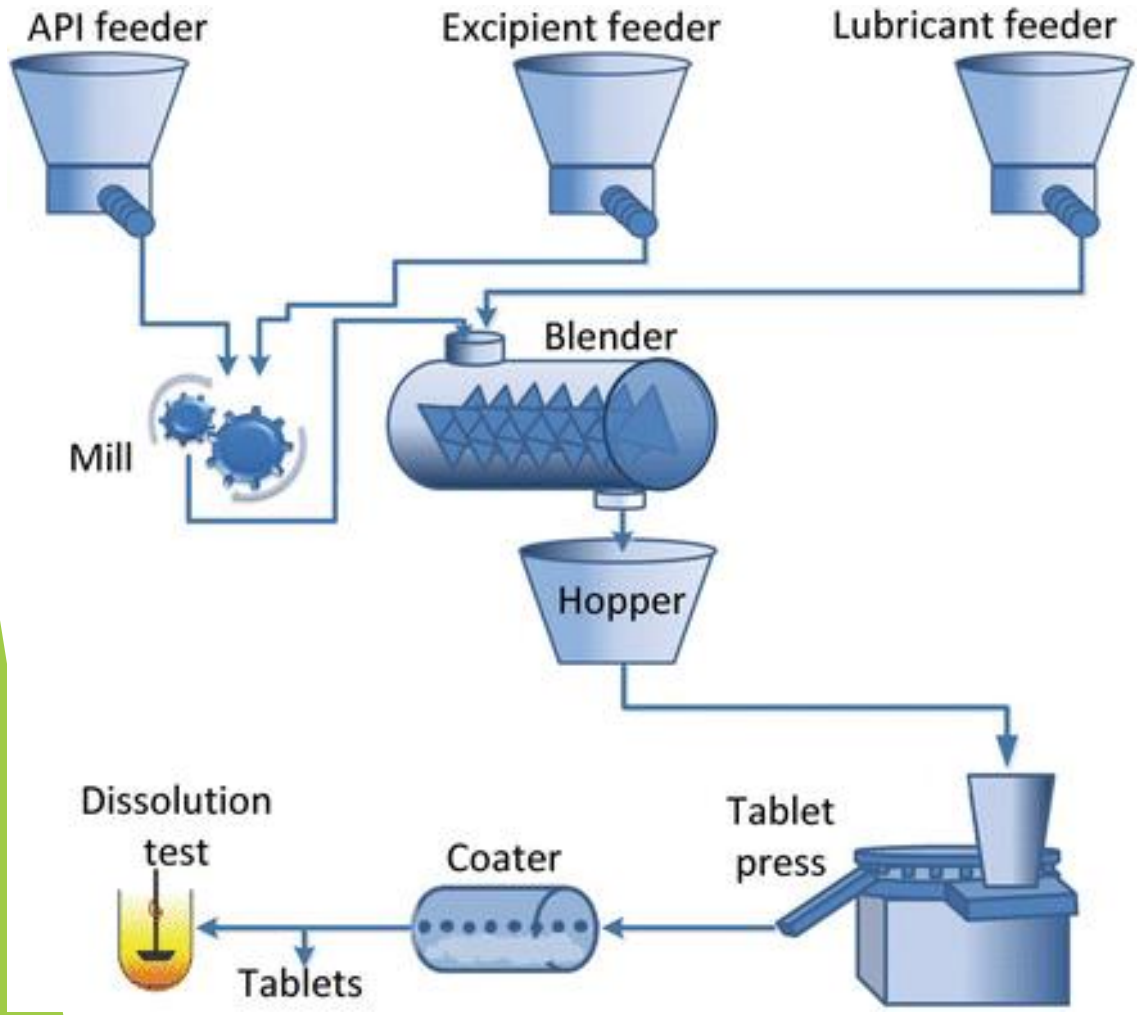
片剂包衣


Outlet Air
Inlet Air
Organic Solvent or
Aqueous Dispersion
Spray
Nozzle
Peristaltic
Pump
Coated
Tablets
Coating
Pan
Coating
Uncoated Core
Tablet Core
Finished
Tablet

包衣锅



现代片剂制作工程


API feeder
Excipient feeder
Lubricant feeder
Blender
Mill
Hopper
Dissolution test
Coater
Tablet press
Tablets


制粒


压片


包衣

现代压片机

旋转式连续压片

An old Cadmach rotary tablet press

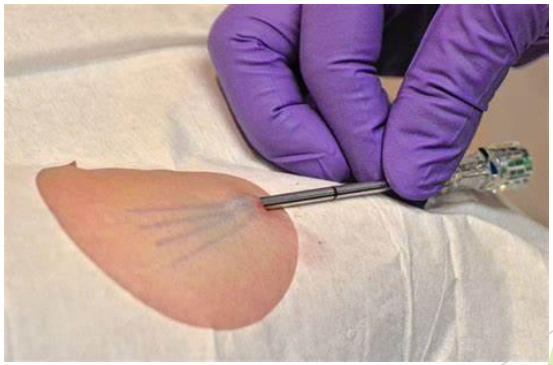
观看制药视频

其它现代药物剂型

注射剂与粉针

喷雾剂

透皮贴片

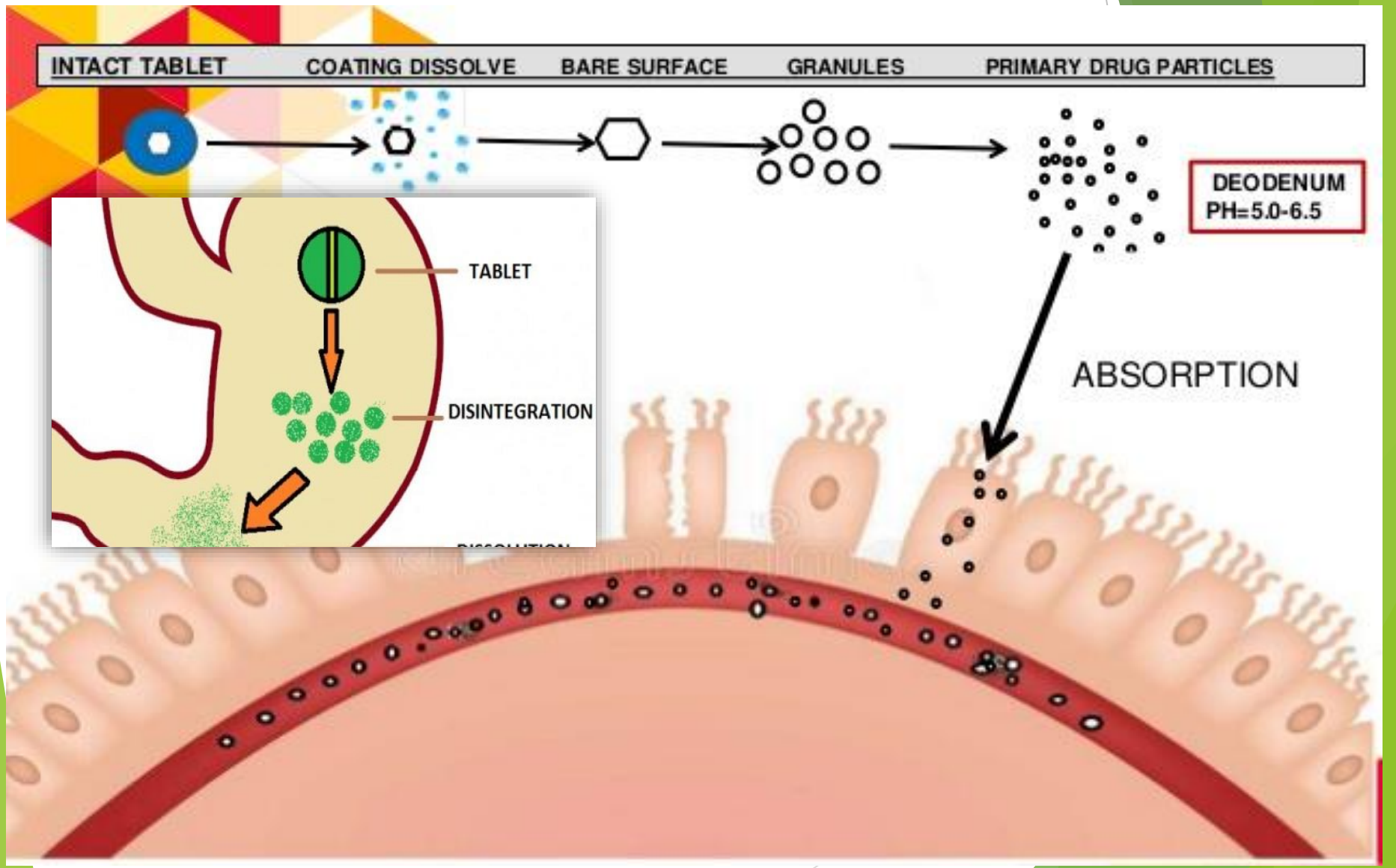


皮下植入剂

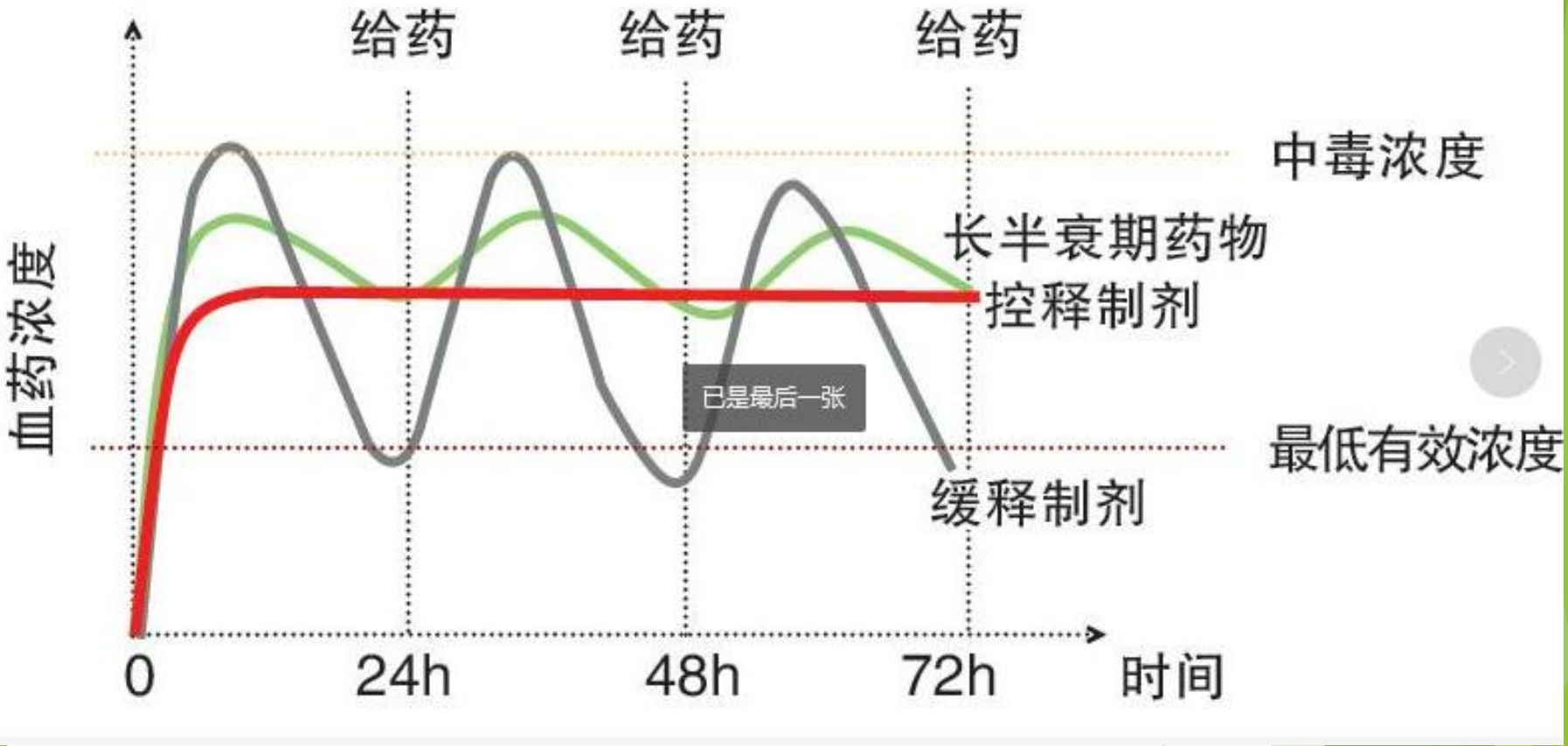
……

第四节：经典剂型介绍

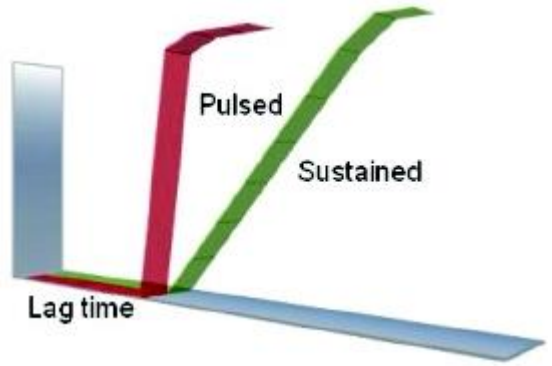
口服片剂与药物吸收

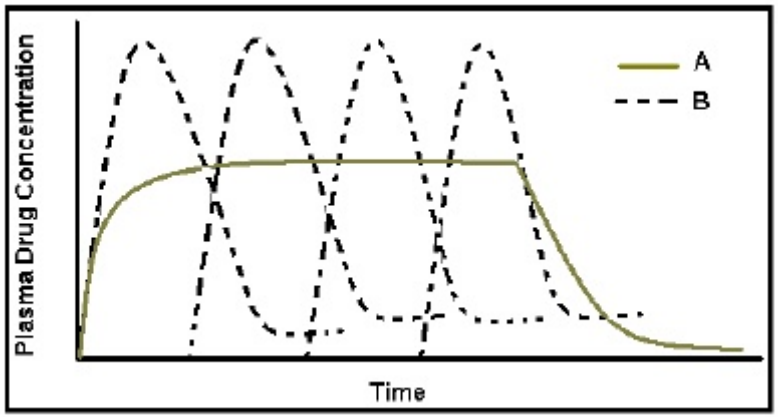

INTACT TABLET
COATING DISSOLVE
BARE SURFACE
GRANULES
PRIMARY DRUG PARTICLES
DEODENUM
PH=5.0-6.5
TABLET
DISINTEGRATION
ABSORPTION

口服片剂 — 缓释和控释

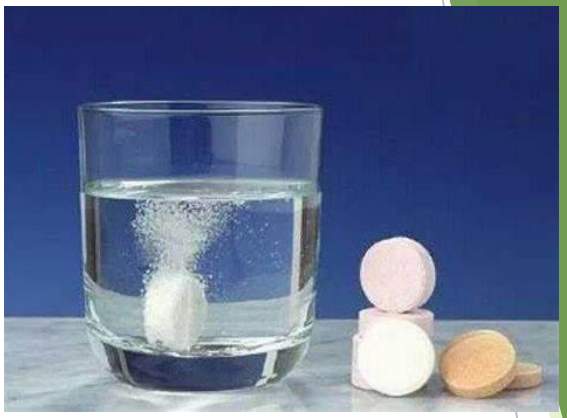

给药
给药
给药
中毒浓度
长半衰期药物
控释制剂
已是最后一张
最低有效浓度
缓释制剂
血药浓度
0
24h
48h
72h
时间

缓释片剂

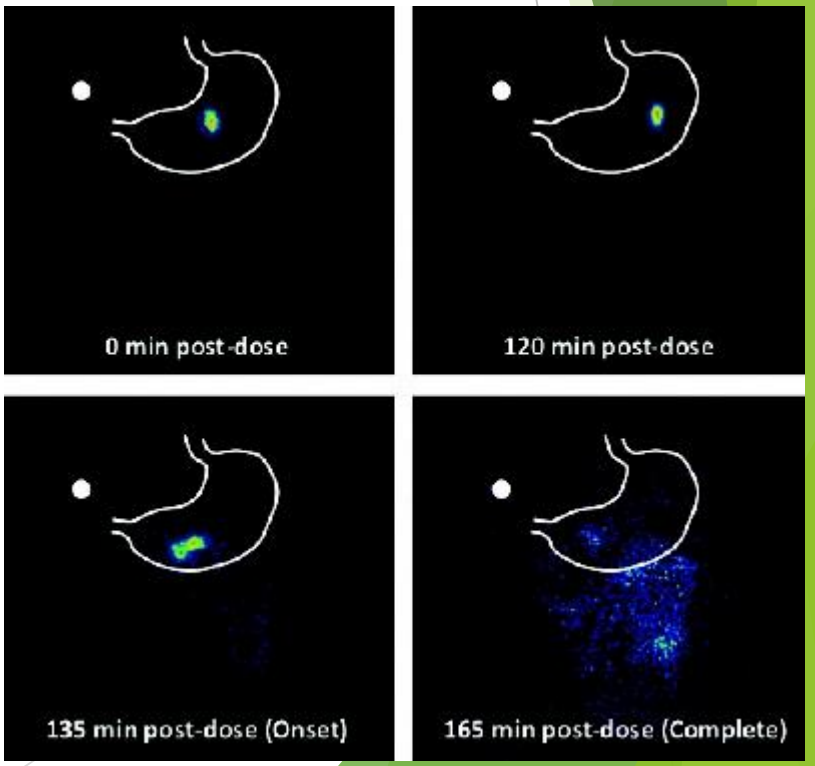




片剂崩解

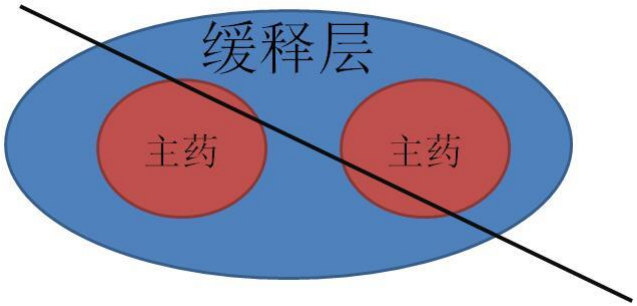


药物释放过程



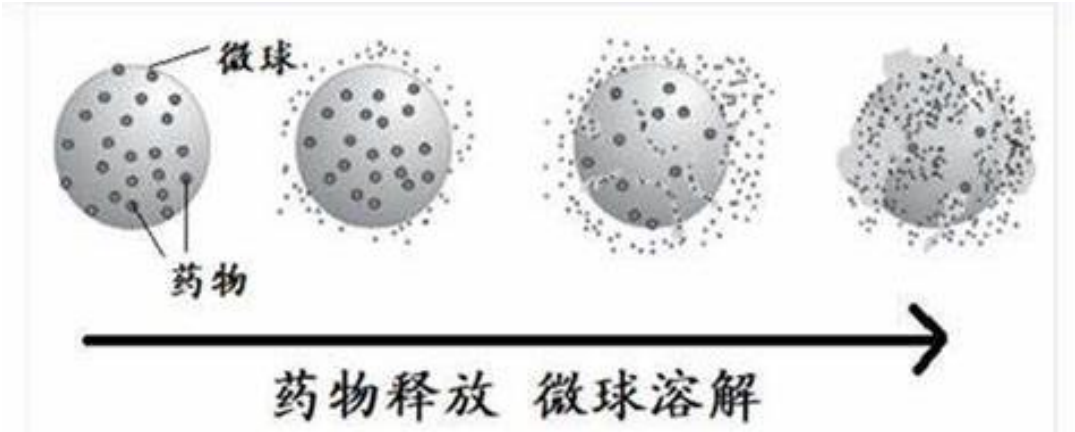
缓释片剂

通过高分子材料包衣，控制药物溶出。



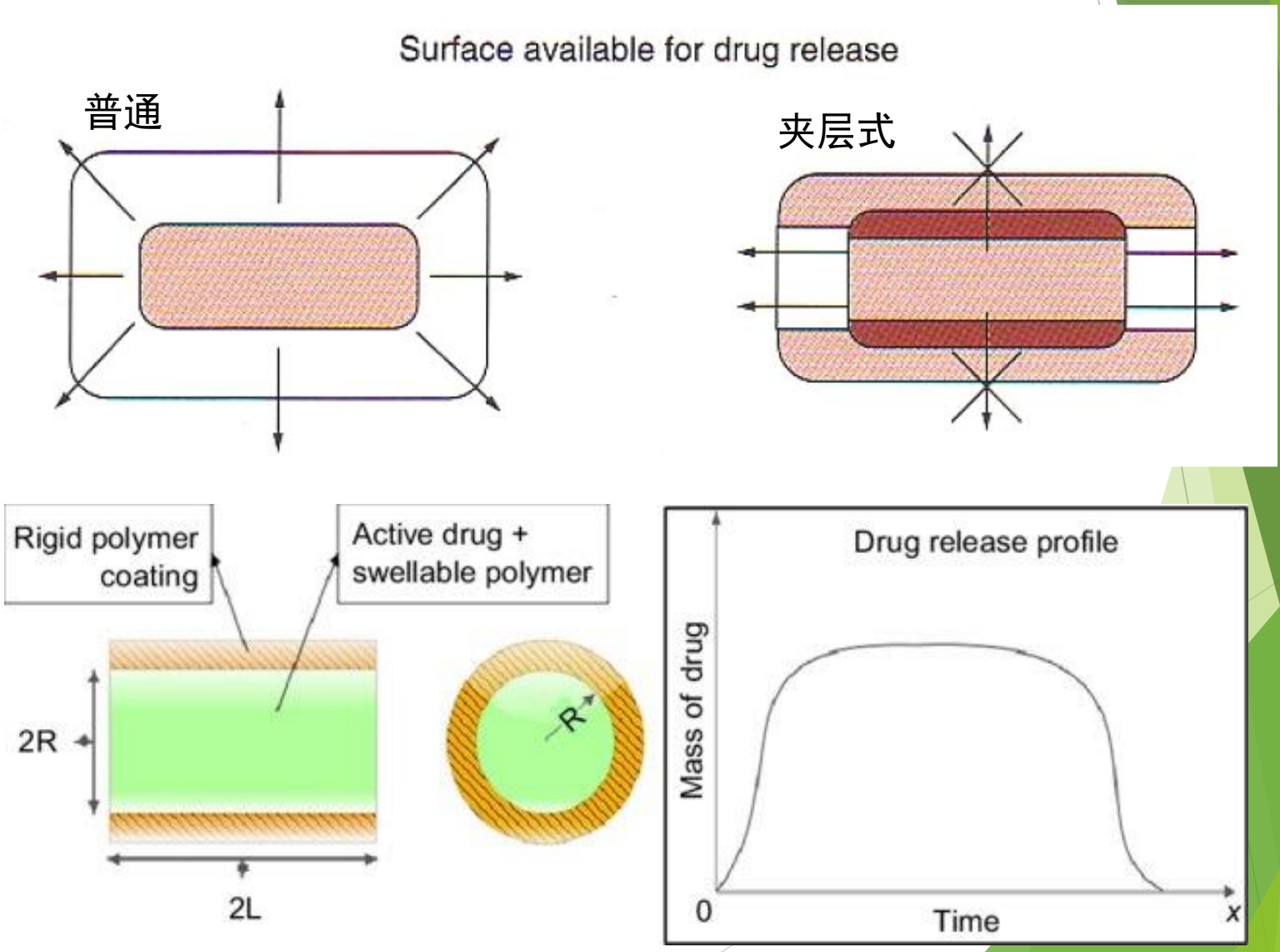
片剂外层包衣

片剂内药物颗粒包衣



缓释片剂

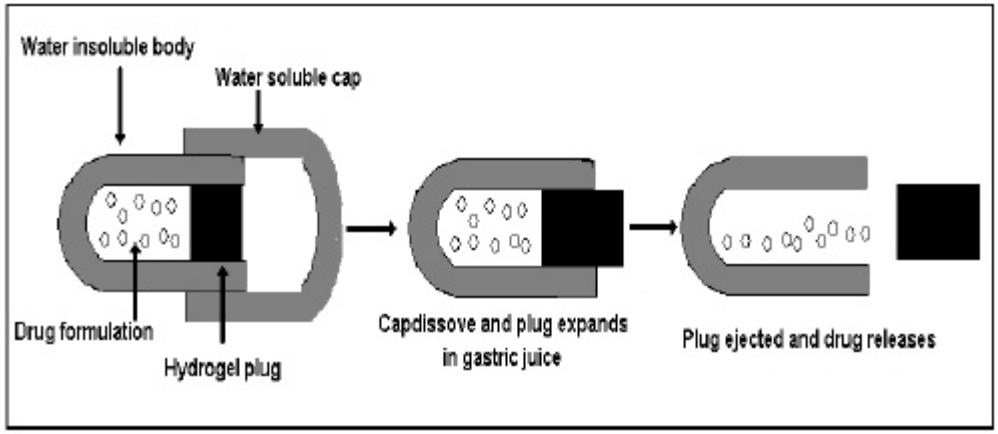
缩小释放面积，缓释药物。

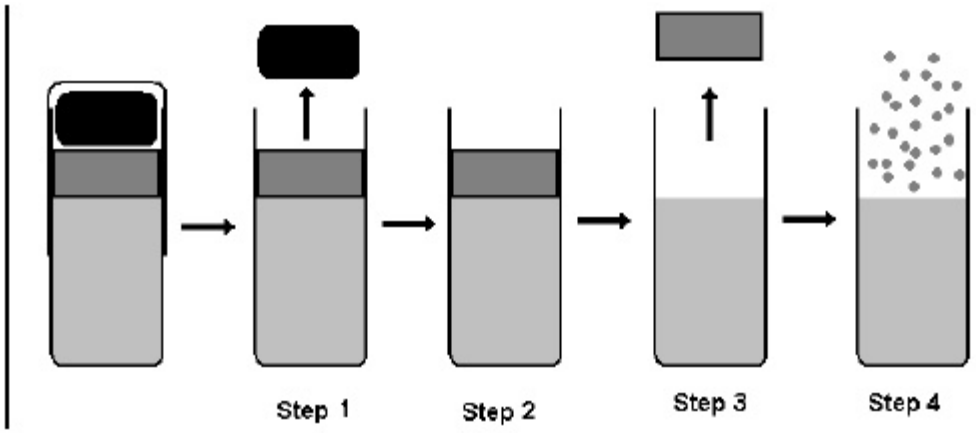


缓释片剂

控制释放帽的打开时间，缓释药物。

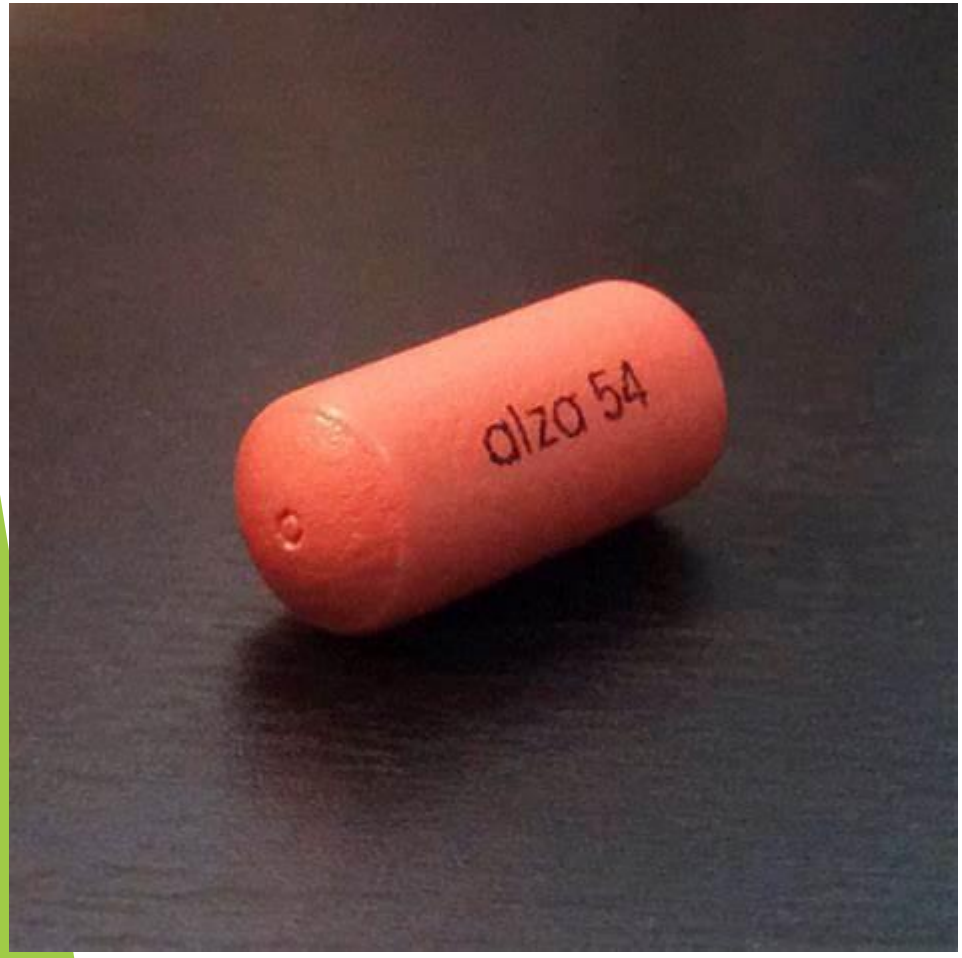
帽式

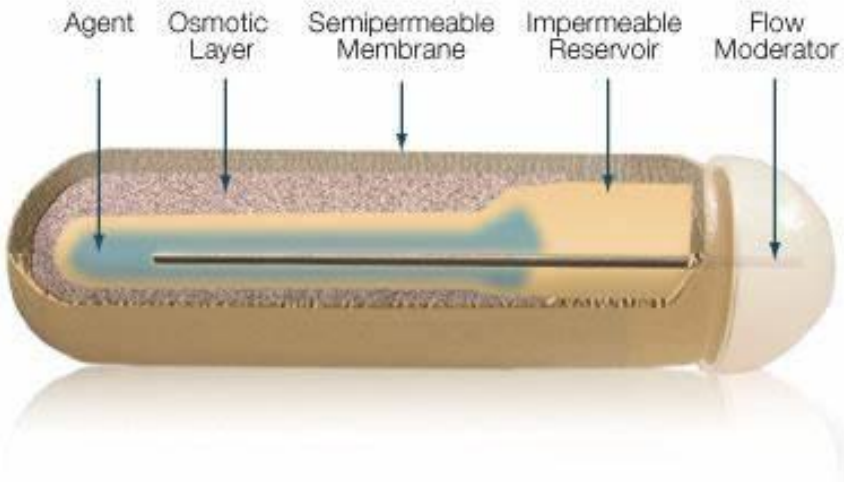


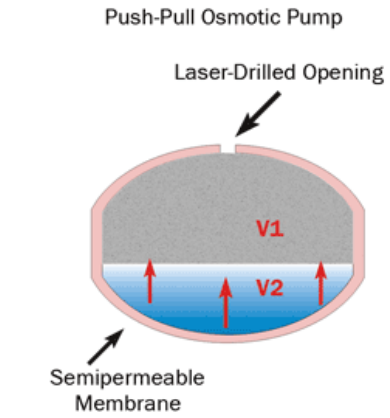


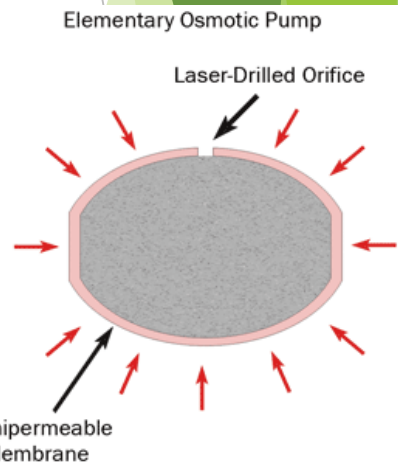
控释 — 渗透泵片剂实现零级释放

Alzet植入式给药泵

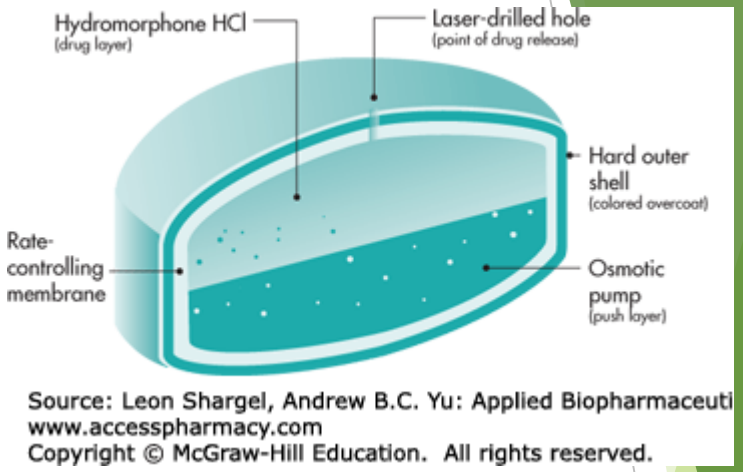




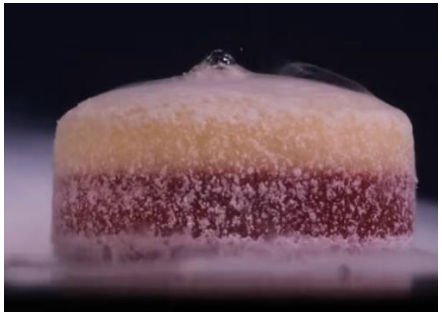




渗透泵片剂实现零级控释

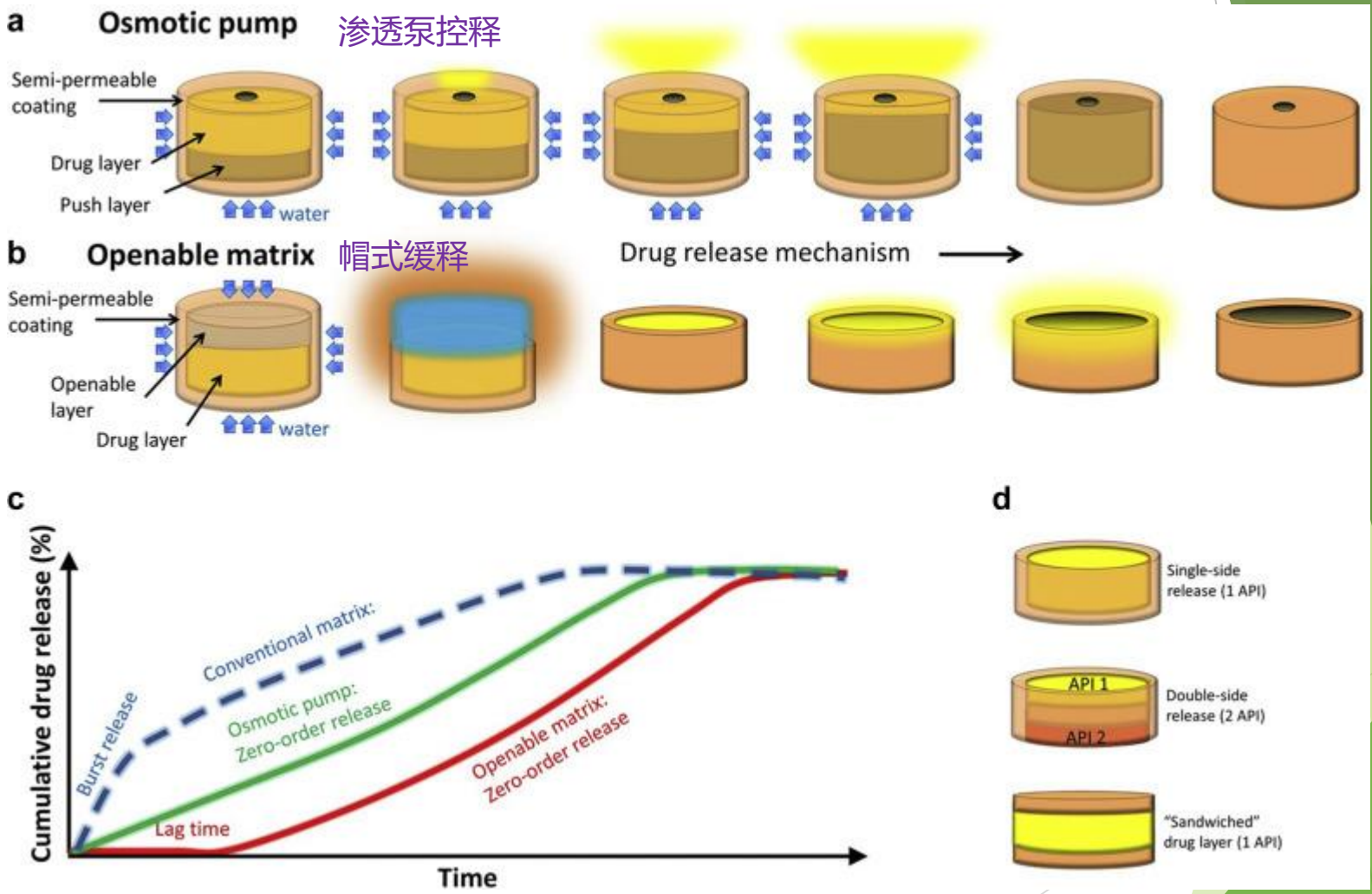


Source: Leon Shargel, Andrew B.C. Yu: Applied Biopharmaceuti
www.accesspharmacy.com



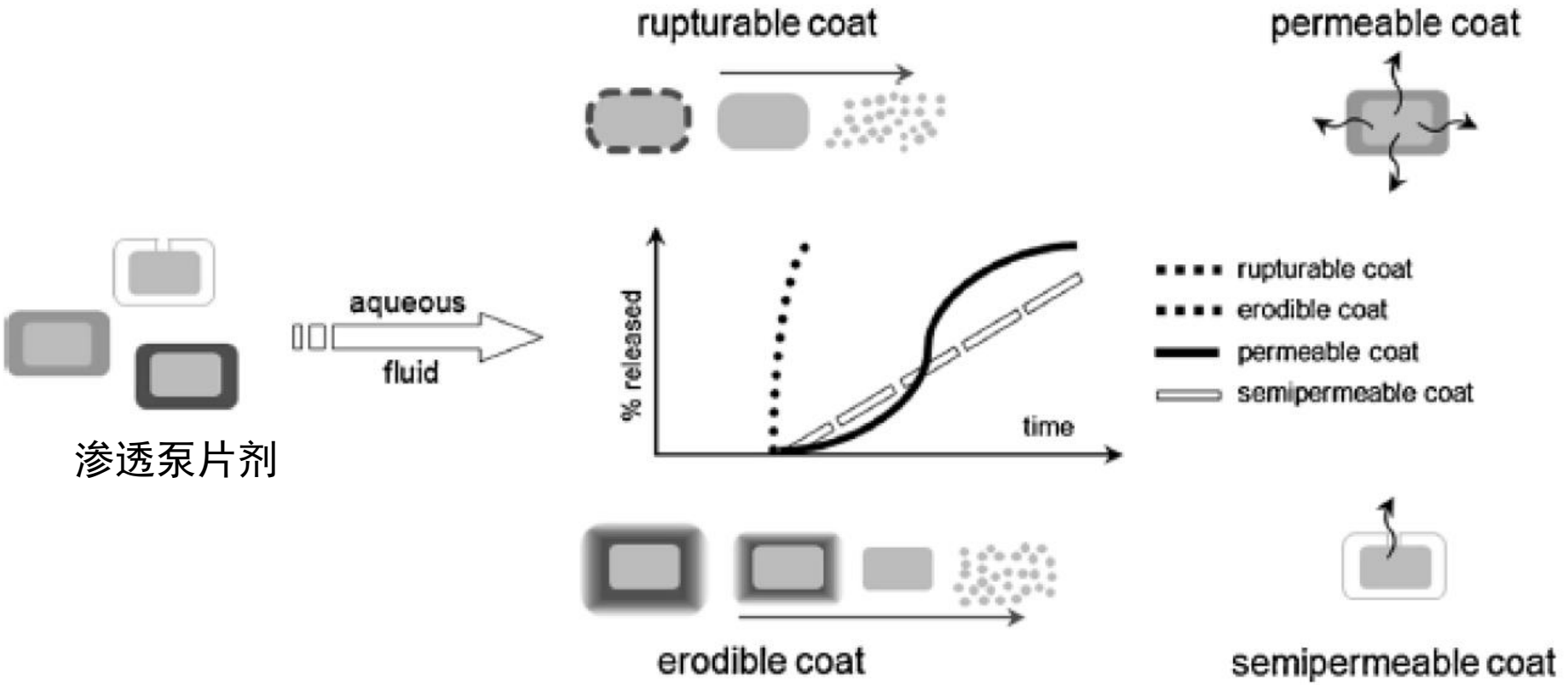
渗透泵控释双层片

渗透泵片剂实现零级控释



缓控释的实现-总结

缓释片剂



Peertechz J Med Chem Res 3(1): 012-022

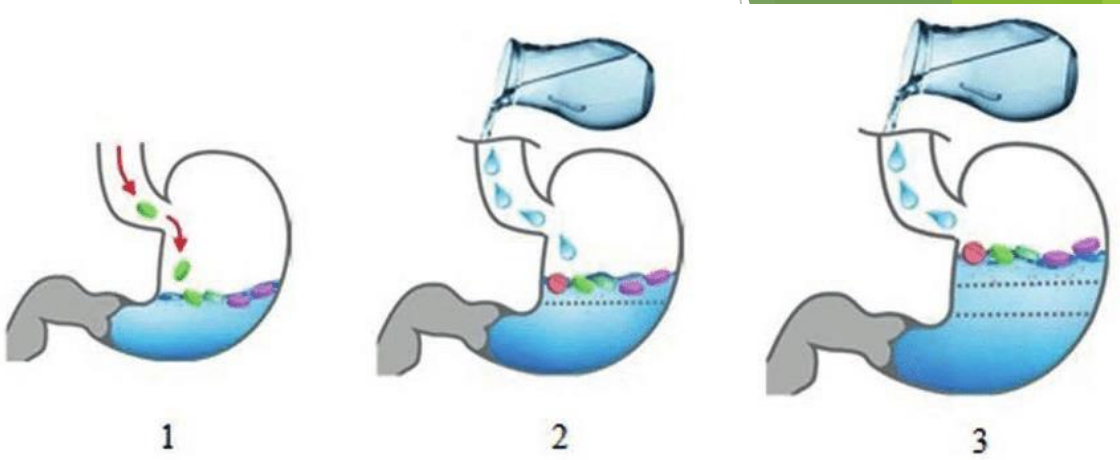
缓控释制剂的剂型分类

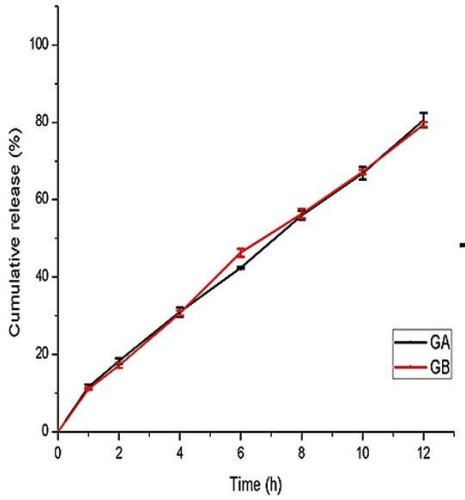
- ✓ 骨架型缓控释制剂 （经典）
  - 溶出型缓控释　　比如微晶药物
  - 扩散型缓控释　　比如帽式、高分子包衣等
  - 置换型缓控释　　比如离子交换型缓释剂
- ✓ 渗透泵缓控释制剂
- ✓ 电子缓控释系统

胃内漂浮片

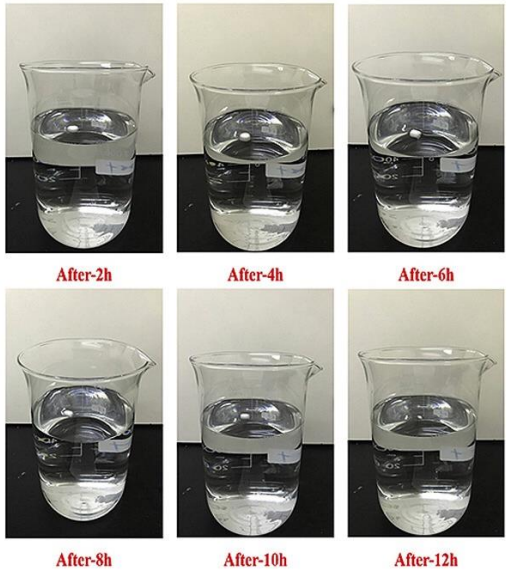
胃滞留技术

- 低密度片剂漂浮
- 胃壁粘贴

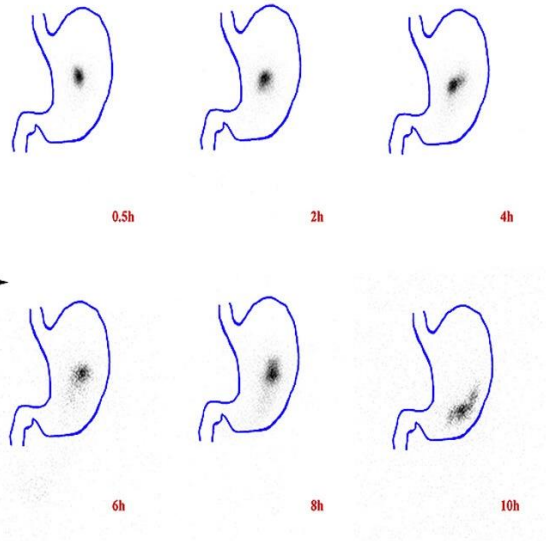




In vitro dissolution studies and release kinetics



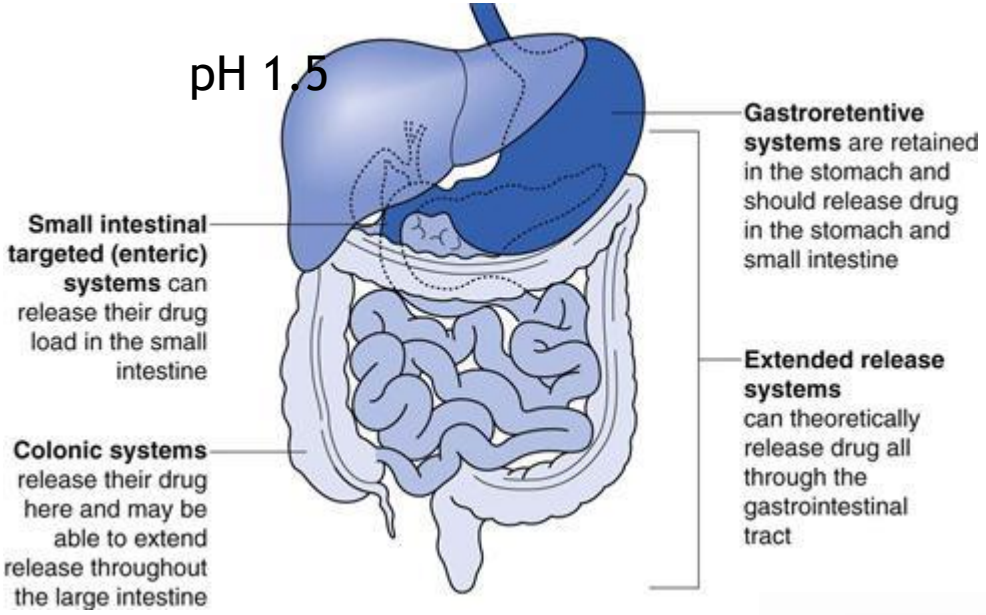
In vitro floating behavior

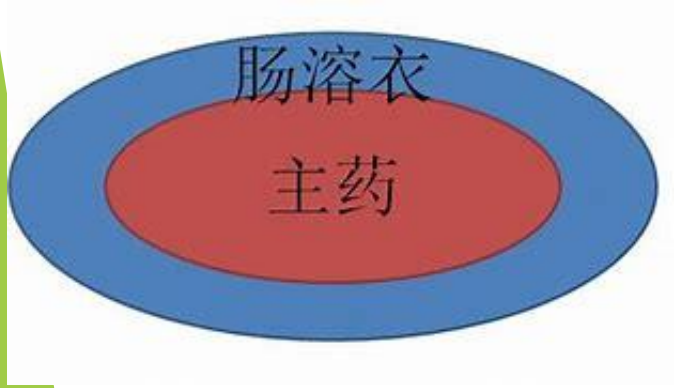


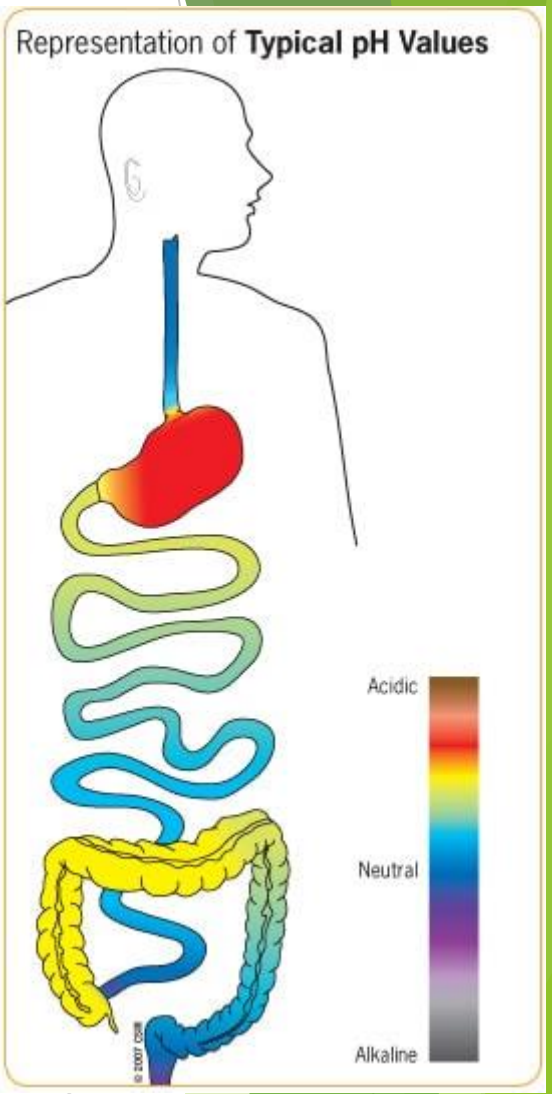
In vivo buoyancy characterization

肠溶片

pH响应型包衣材料，实现在肠道定点药物释放



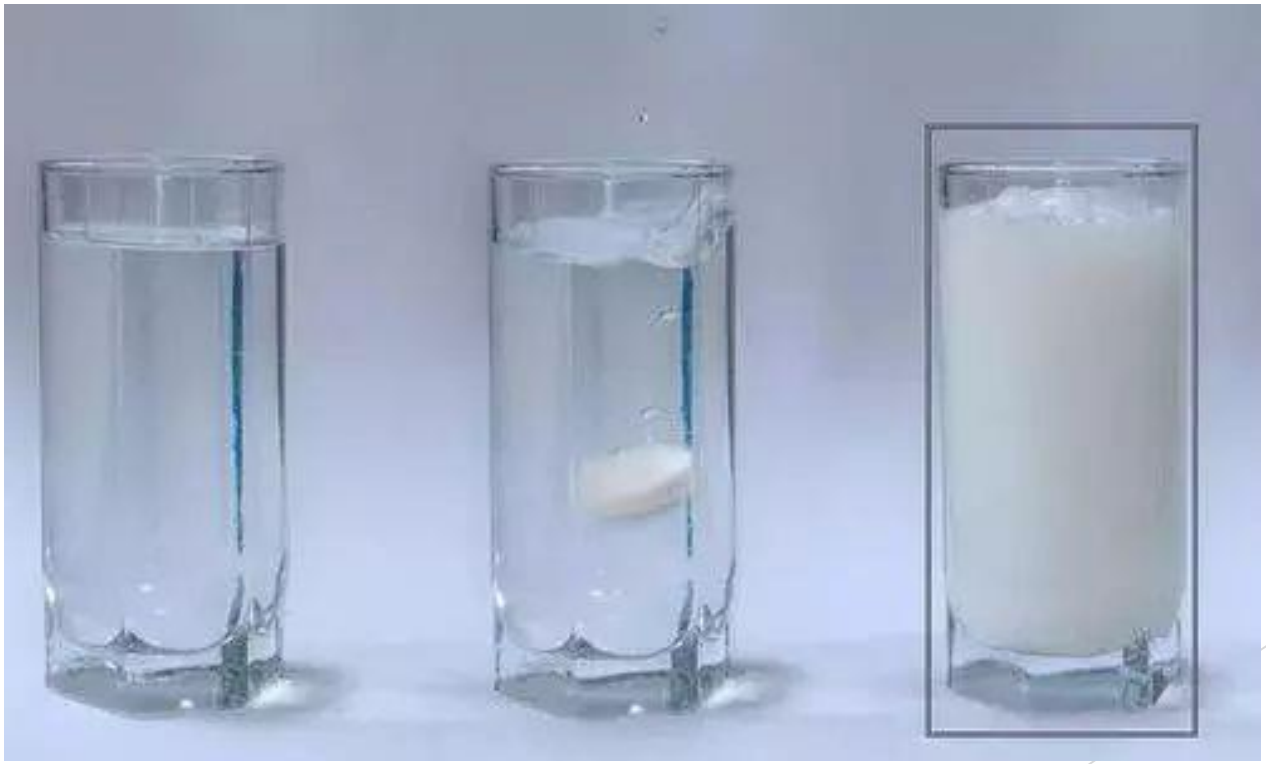




泡腾片

压片辅料为有机酸和无机碱（NaHCO3），遇水后释放大量CO2，加快片剂崩解和药物释放。

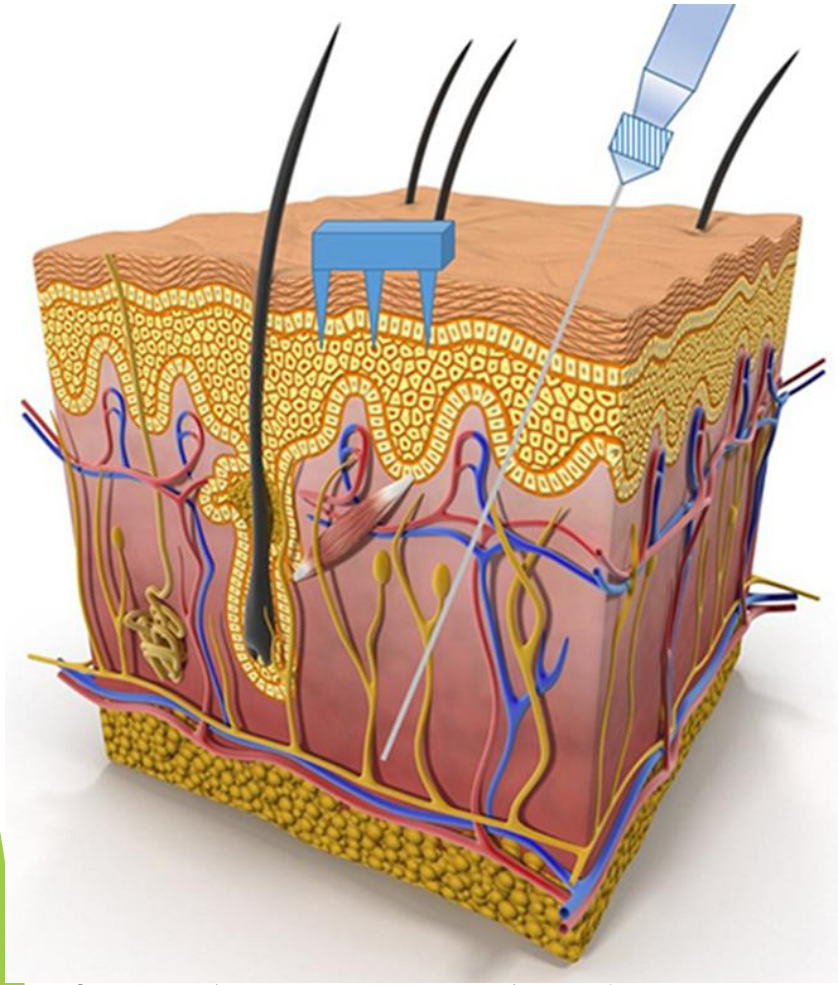
特点：见效快



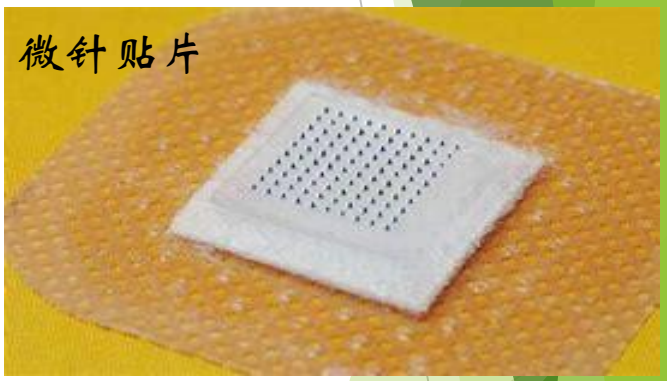
维生素泡腾片

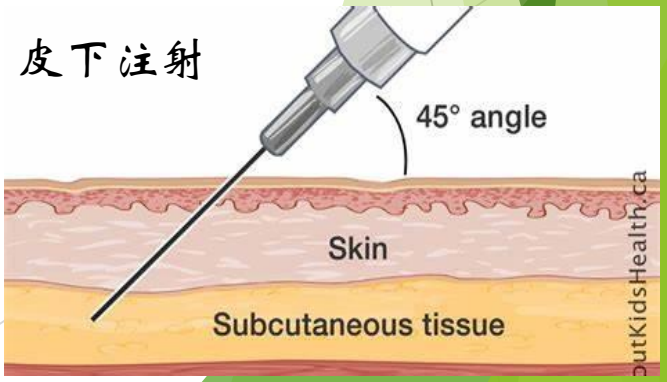
第五节：药剂学国际前沿

透皮给药与微针



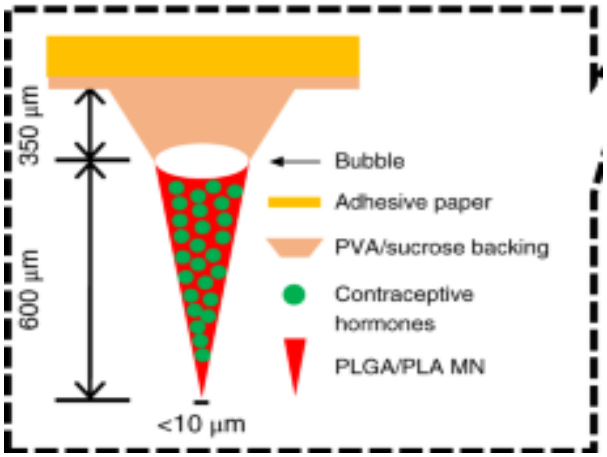
皮肤的角质层阻碍药物吸收入血

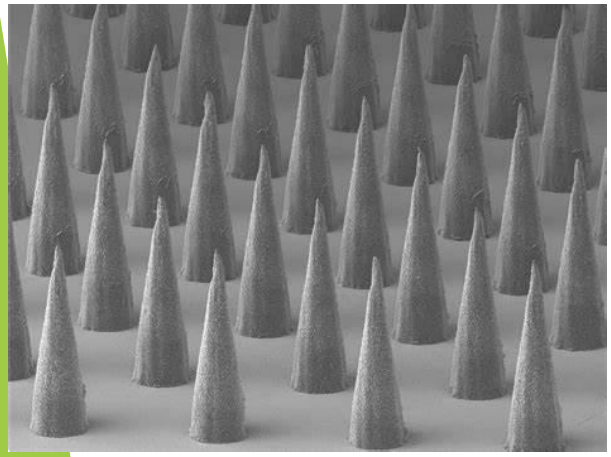


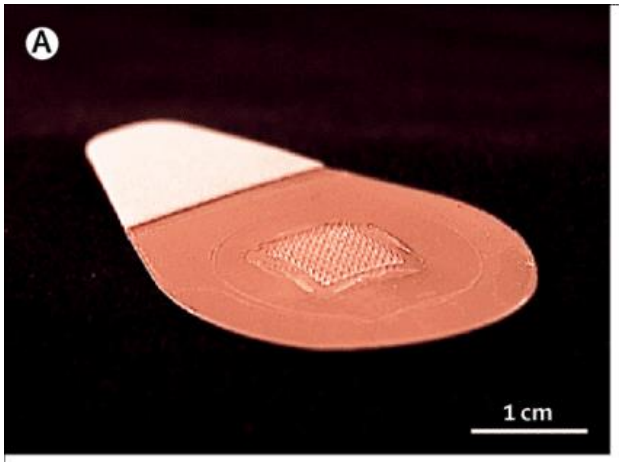


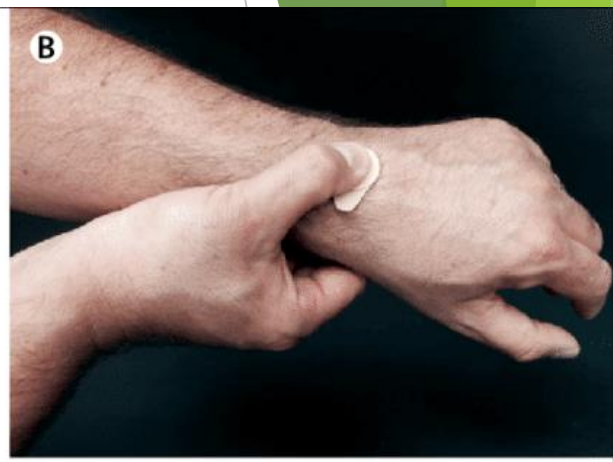
微针

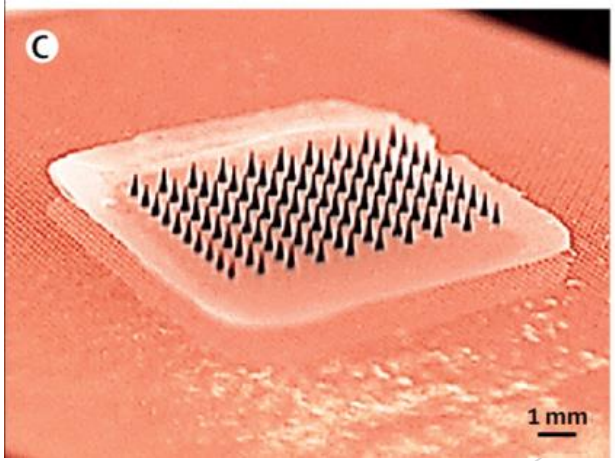
微针通过可降解的高分子材料针尖，穿透皮肤角质层，释放药物入皮下细胞层。材料可降解，针尖很短，无明显痛感。

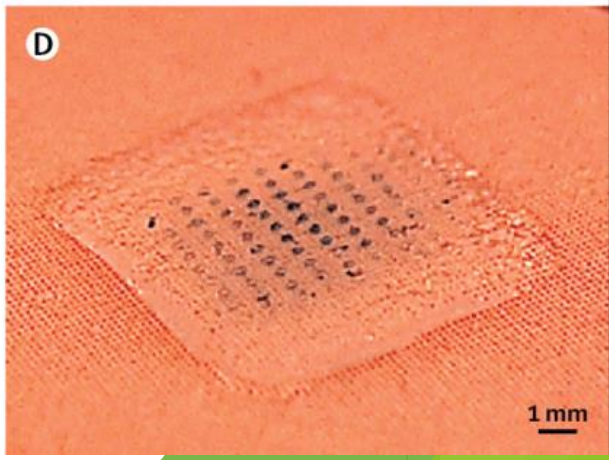






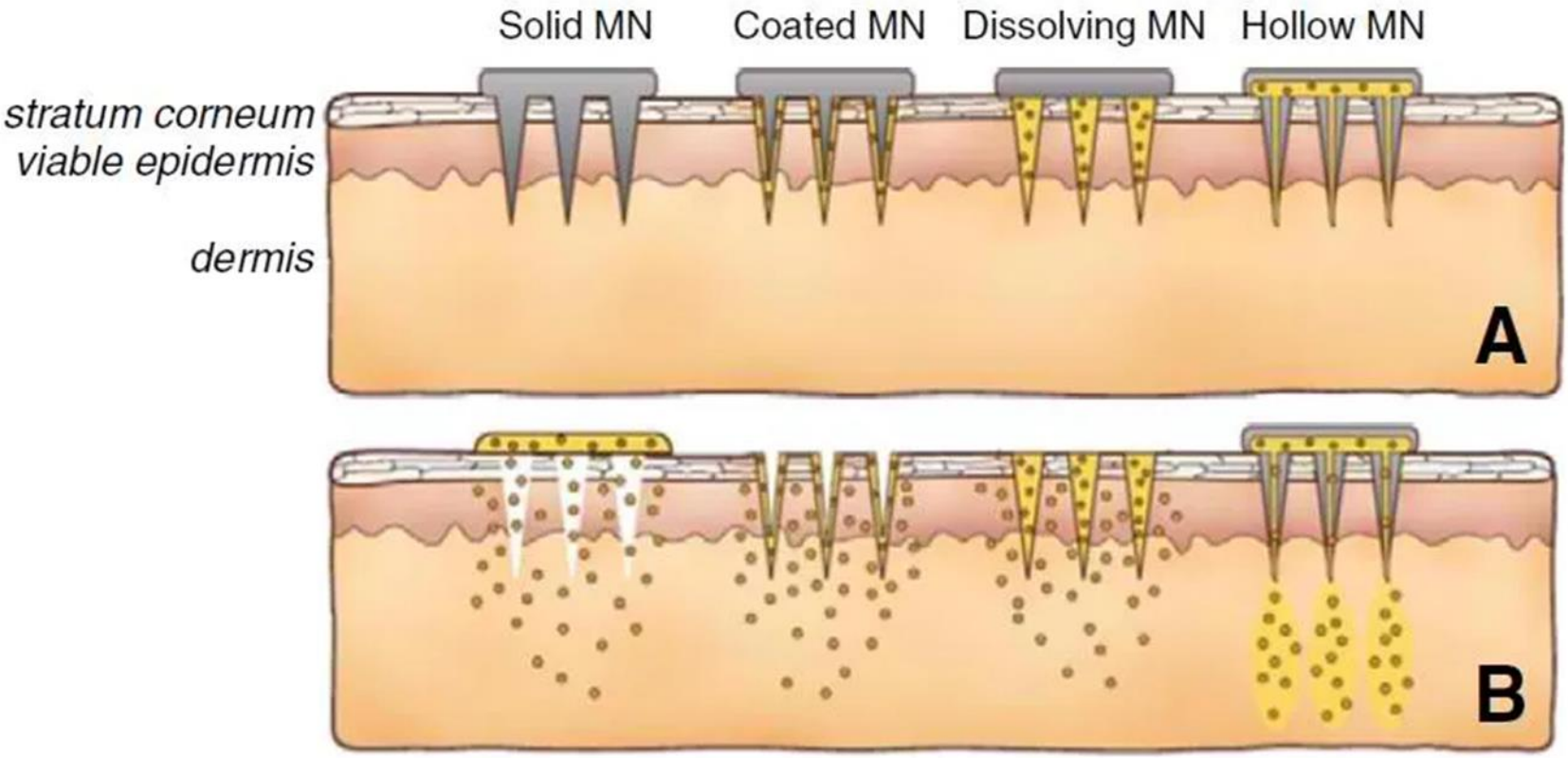






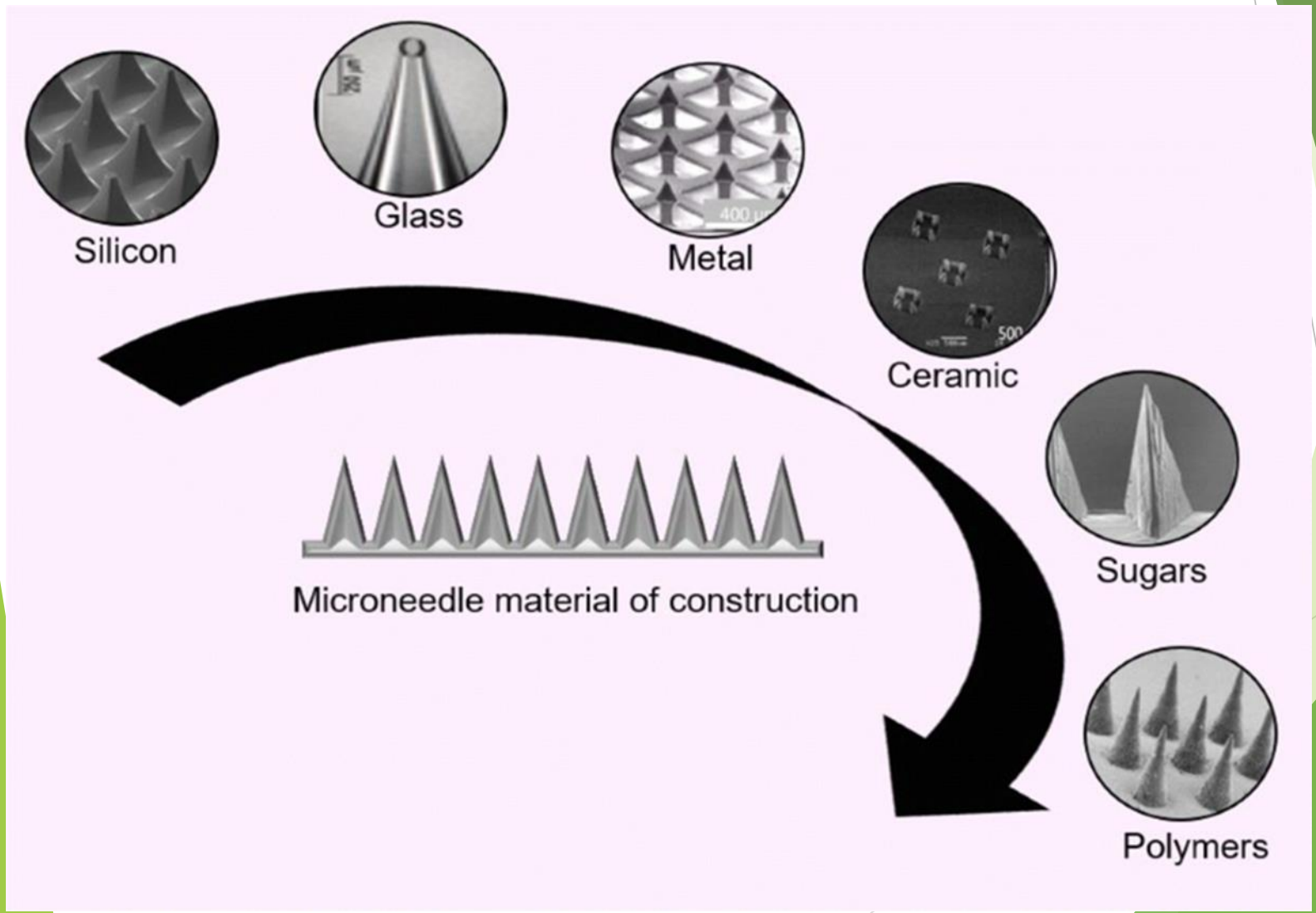
微针贴片的递送原理

微针的多种释药模式



微针贴片的制作

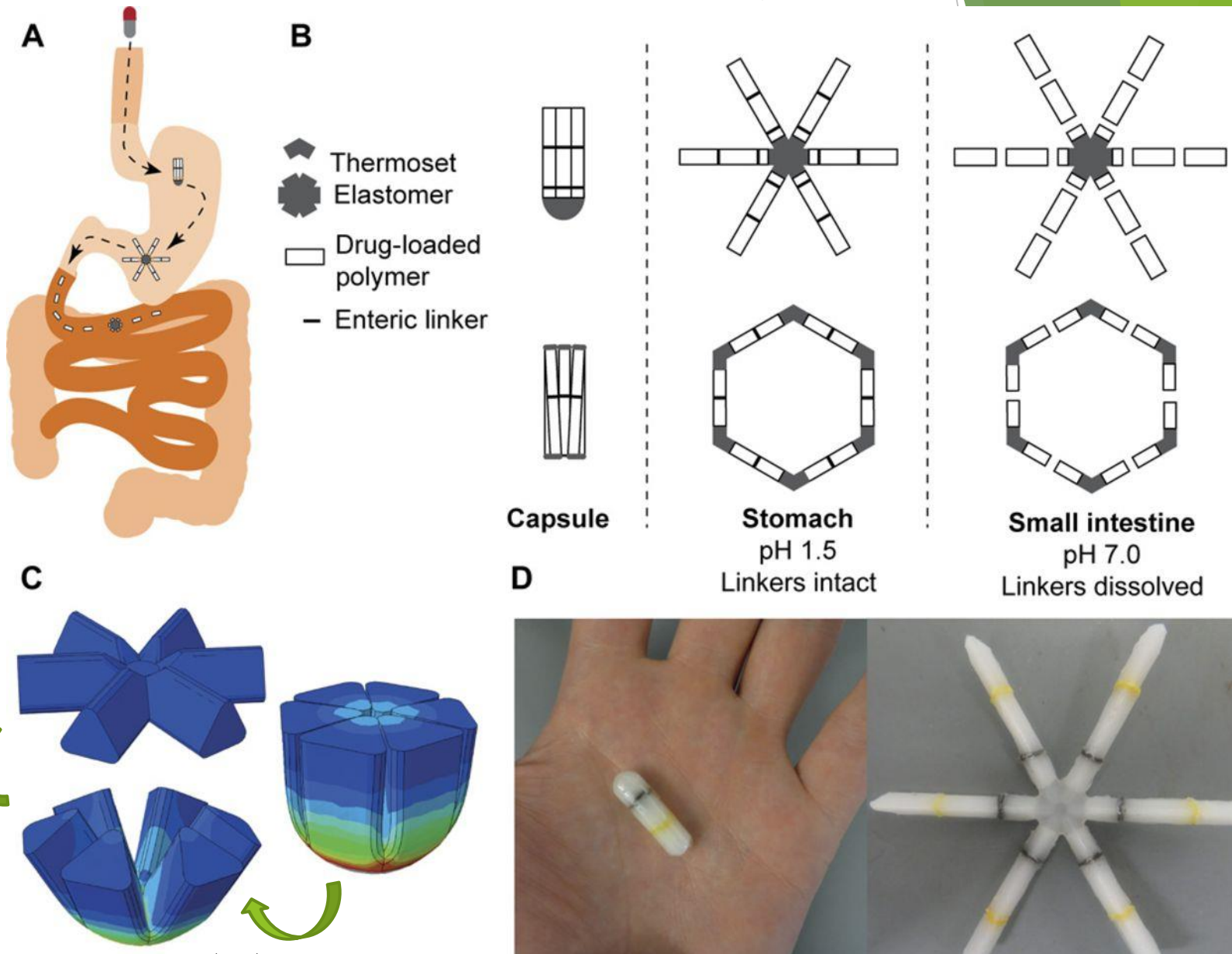
光刻技术制备微针



可变形片剂

肠道释放药物14天

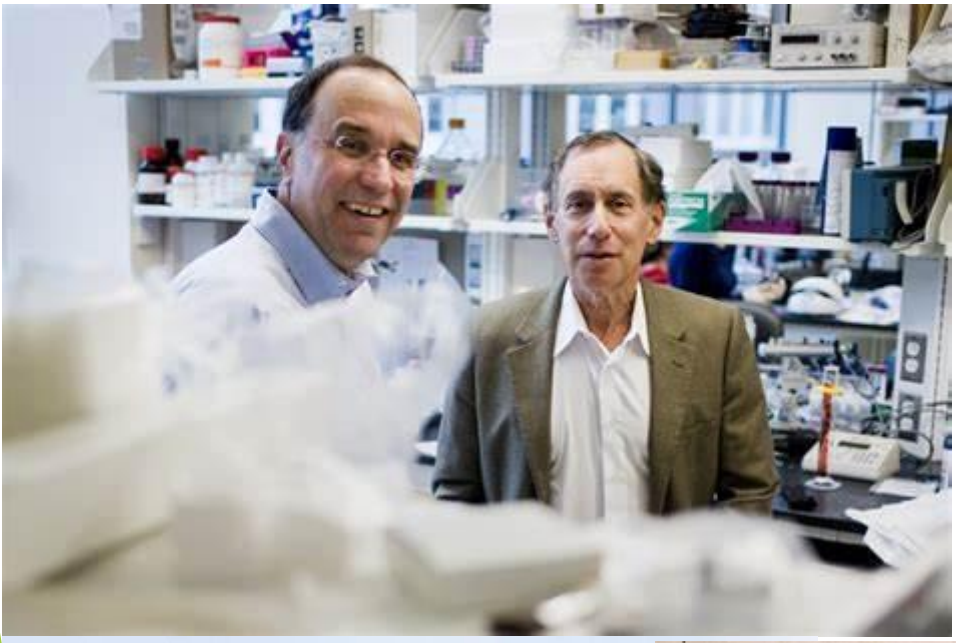
变形片在胃中展开，卡在幽门处，从而避免被消化系统排出，实现长期释药。



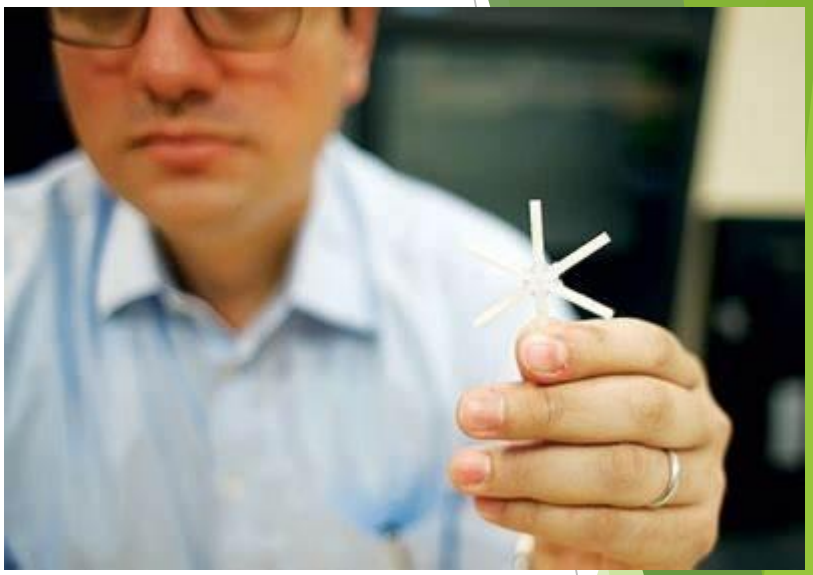
Science translational medicine 8(365):365ra157-365ra157

可变形片剂

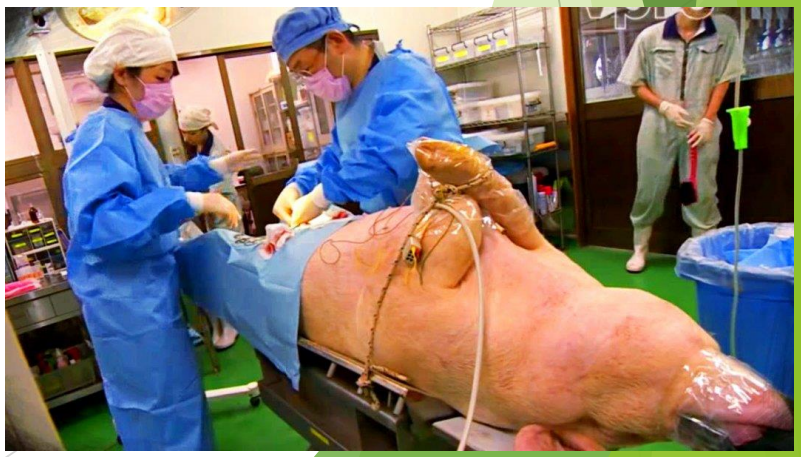
Prof Giovanni Traverso和Prof Robert Langer



Prof Giovanni Traverso展示Stella片剂

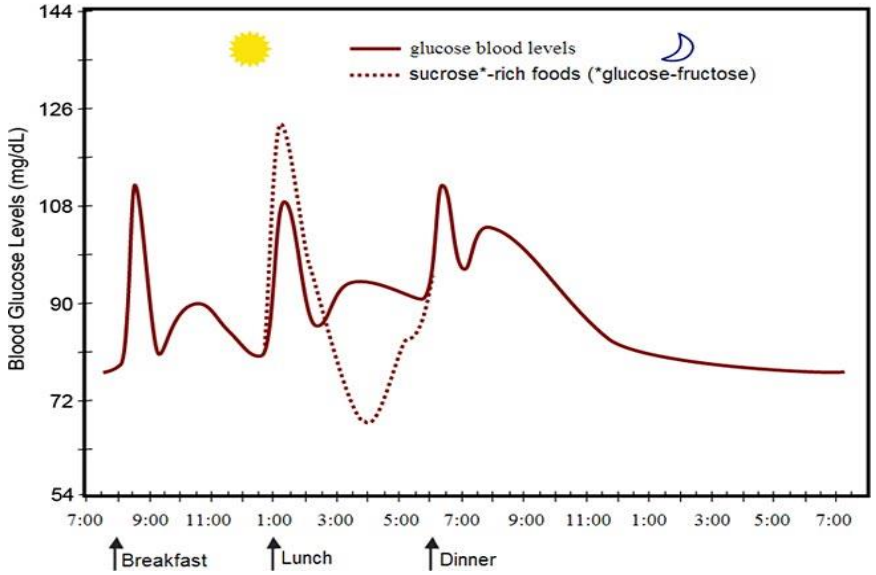


实验猪，价值1万美元/头



胰岛素闭环递送系统 Closed loop system

健康人的进食与血糖波动



血糖标尺与范围

FASTING BLOOD GLUCOSE LEVEL CHART

Level /Risk	mg/dL
Dangerously high	315+
High	280
High	250
High	215
Borderline	180
Borderline	150
Borderline	120
Normal	72-108
Low	70
Dangerously low	50

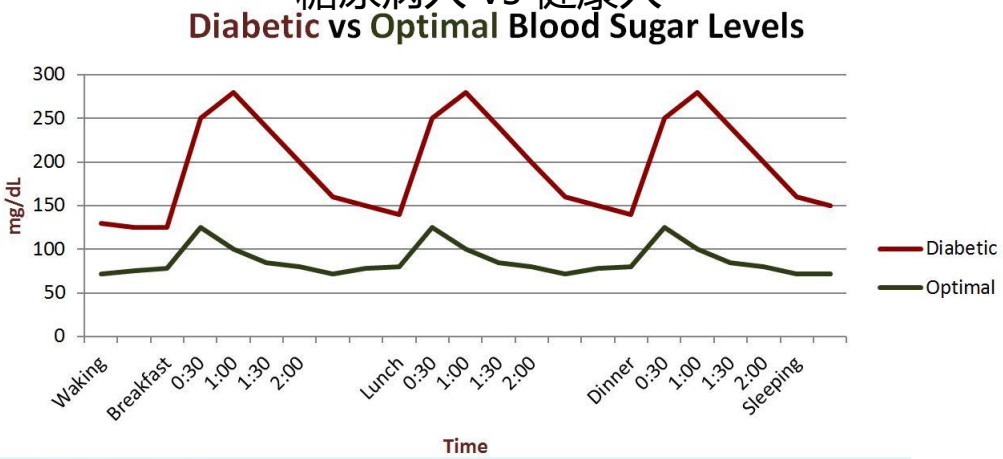
DIABETES > 125
高血糖并发症

PREDIABETES 100-125

NORMOGLYCEMIA 70-99

HYPOGLYCEMIA < 70
低血糖昏迷

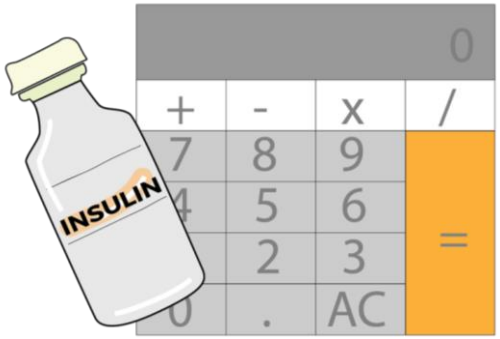
糖尿病人 vs 健康人



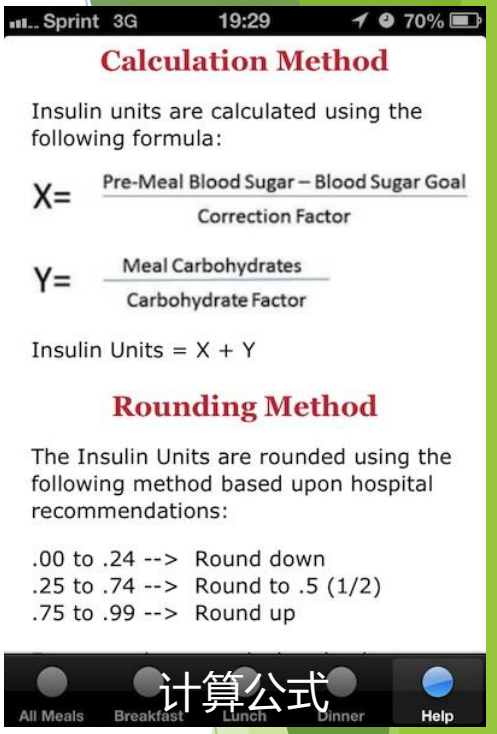
胰岛素闭环递送系统

糖尿病开环注射治疗 （open loop therapy）

测血糖



计算胰岛素剂量



计算公式

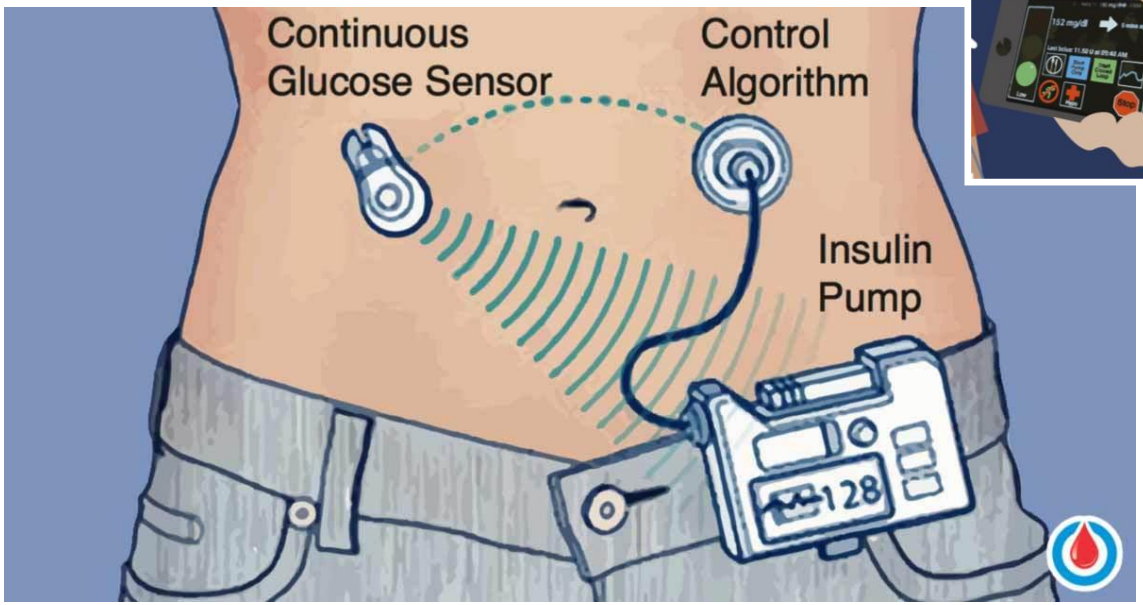
胰岛素注射准备

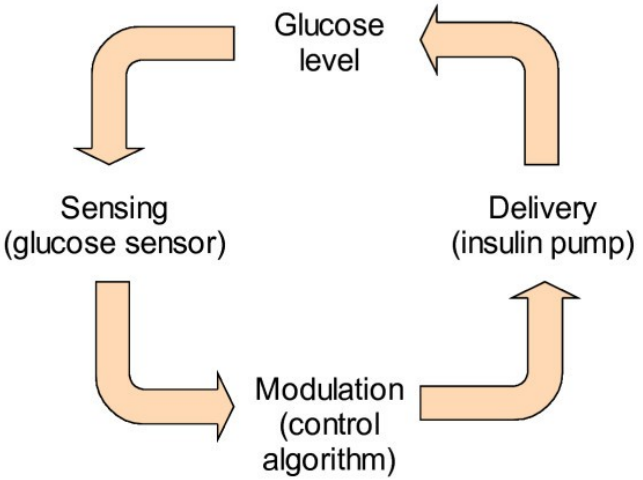
胰岛素准确剂量吸取

皮下注射

胰岛素闭环递送系统

胰岛素智能注射泵 Closed loop system

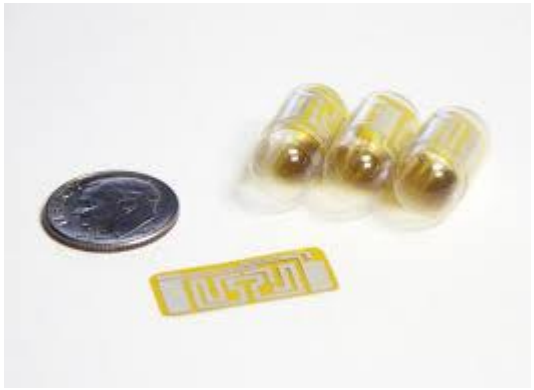


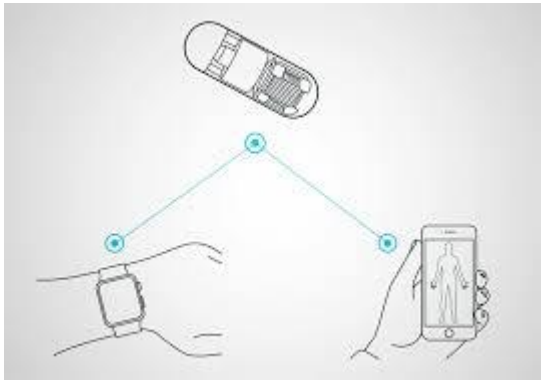


Tight Glycemic Control

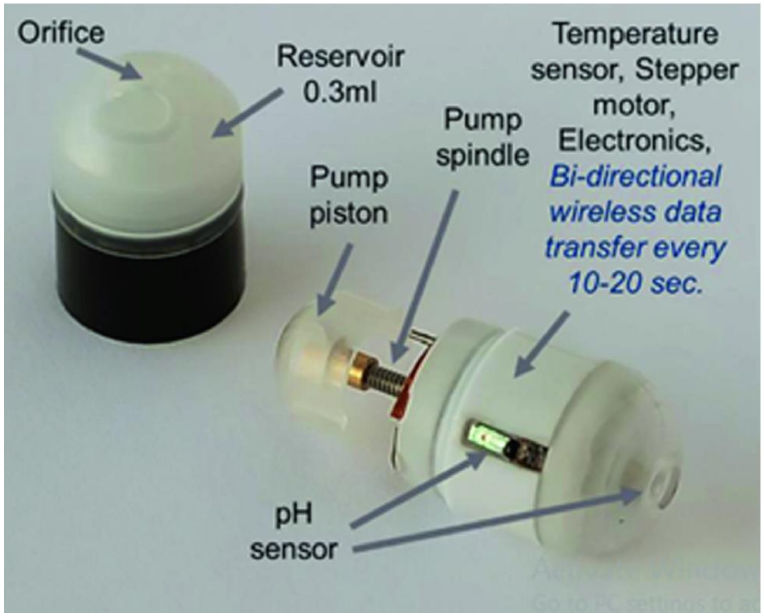
电子药片

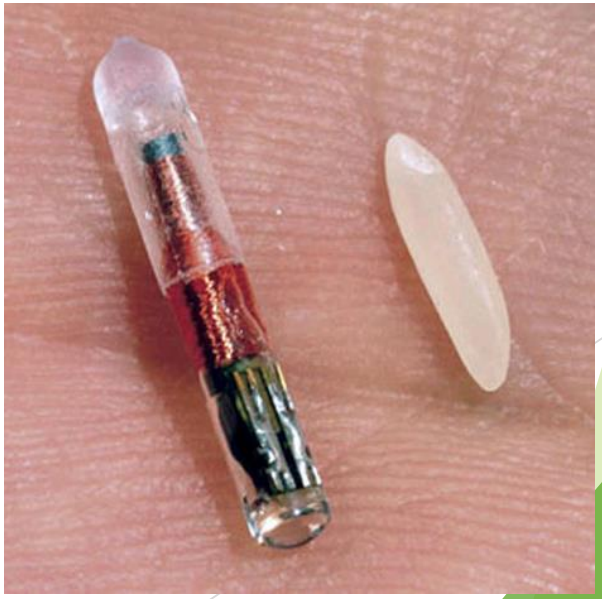

if(parameters.contains(
hql += " and p.name =
}
if(parameters.contains("age")){
hql += " and p.age = :age
}
Flags Metric
255.255.255.255 UH 0
255.255.255.255 UH 0
255.255.255.0 U 0
UG 0
Flags
255.255 UH 0





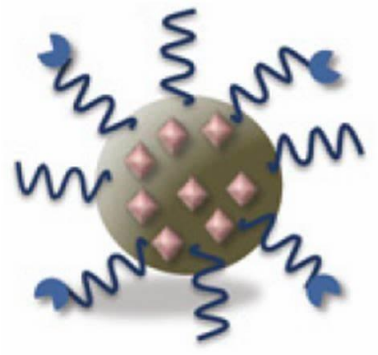
以植入剂为主


Orifice
Reservoir
0.3ml
Pump
spindle
Temperature
sensor, Stepper
motor,
Electronics,
Bi-directional
wireless data
transfer every
10-20 sec.
Pump
piston
pH
sensor

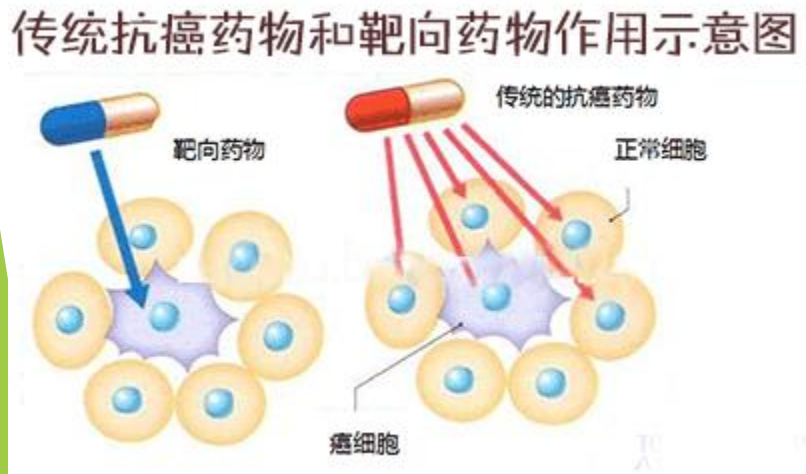


现代靶向制剂

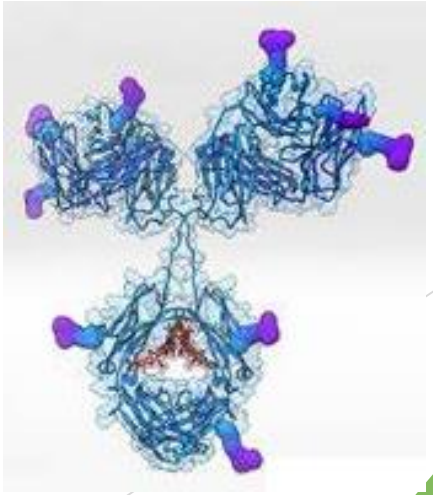
■ 纳米靶向制剂



■ 小分子靶向药物



■ 抗体类靶向



■ 其它

抗体 - 最成功的靶向药物

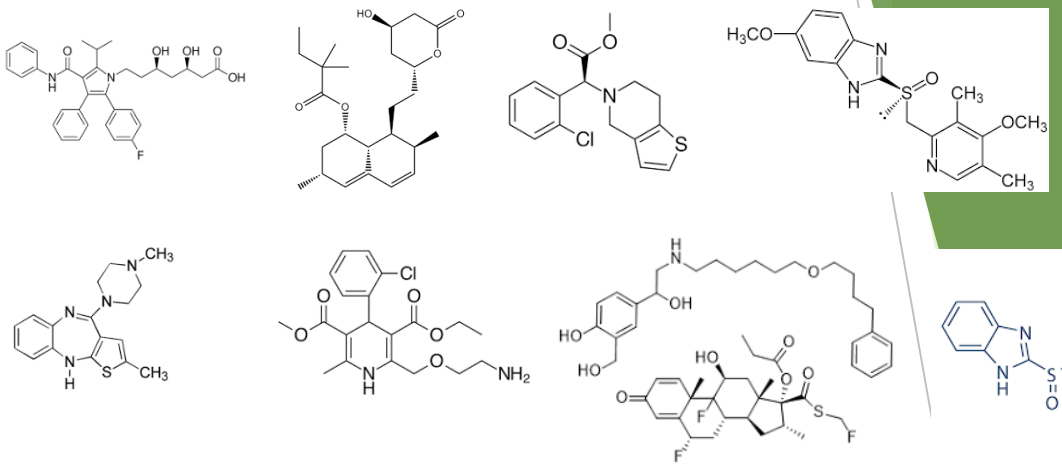
2004年全球最畅销药物

The blockbusters 5

Top ten brands, global sales, 2004, $bn

Lipitor (cholesterol-lowering)	12.0
Zocor (cholesterol-lowering)	5.9
Plavix (anti-clotting)	5.0
Nexium (anti-ulcerant)	4.8
Zyprexa (anti-psychotic)	4.8
Norvasc (anti-hypertensive)	4.8
Seretide/Advair (anti-asthma)	4.7
Erypo (blood-cell booster)	4.0
Prevacid (anti-ulcerant)	3.8
Effexor (anti-depressant)	3.7

Source: IMS Health

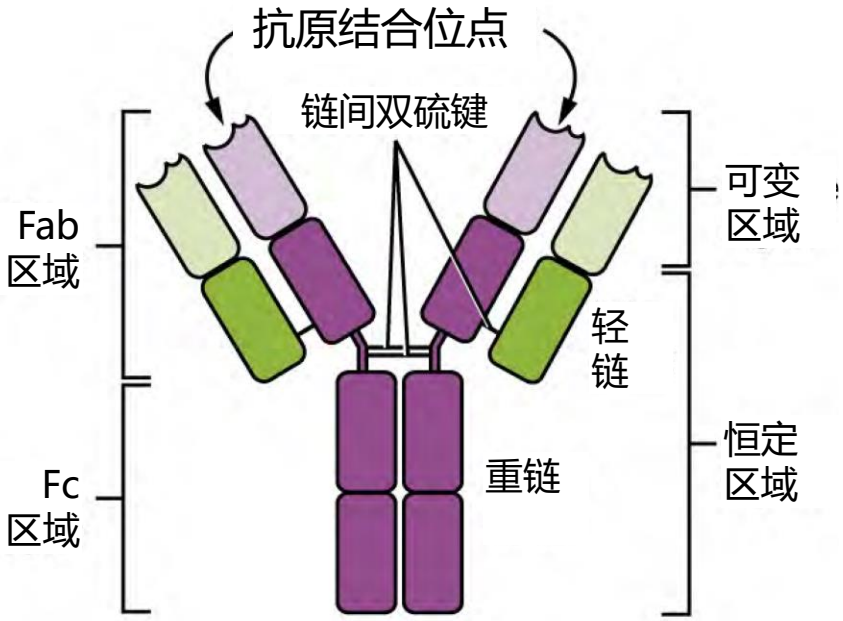


修美乐-HUMIRA
阿达木单抗-Adalimumab
靶向肿瘤坏死因子(TNF)

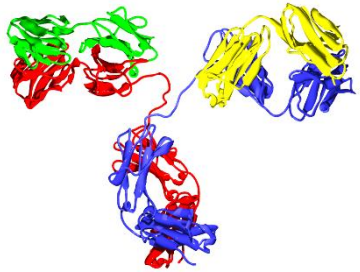
2019年全球最畅销药物

排名	销售额（亿美元）	药物	中文名	公司	适应症	类型
1	208.83	Humria	修美乐	Abbvie	自身免疫性疾病	单抗
2	110.87	Revlimid	瑞复美	Celgene	多发性骨髓瘤等	小分子
3	101.84	Eliquis	艾乐妥	BMS/Pfizer	抗血凝剂	小分子
4	100.07	Keytruda	可瑞达	MSD	多种肿瘤	单抗
5	79.58	Opdivo	欧狄沃	BMS	多种肿瘤	单抗
6	78.56	Eylea	艾力雅	Bayer/Regeneron	年龄相关黄斑变性	融合蛋白
7	73.32	Enbrel	恩利	Amgen/Pfizer	自身免疫性疾病	融合蛋白
8	73.2	Imbruvica	亿珂	J&J/Abbvie	淋巴瘤等	小分子
9	68.11	Avastin	安维汀	Roche	结肠癌等多种癌症	单抗
10	65.99	Herceptin	赫赛汀	Roche	乳腺癌等多种癌症	单抗

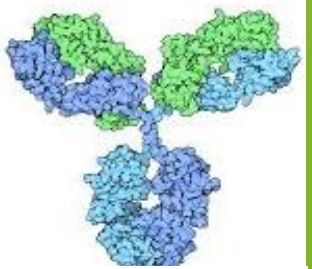
抗体的基本结构



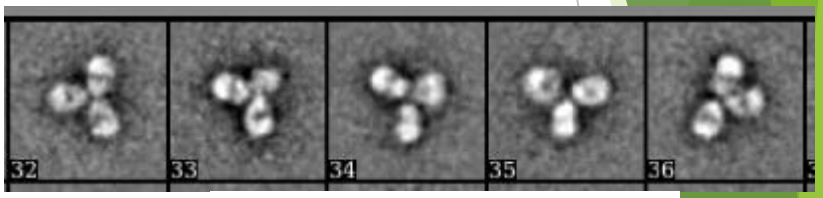
抗体的常见结构示意图



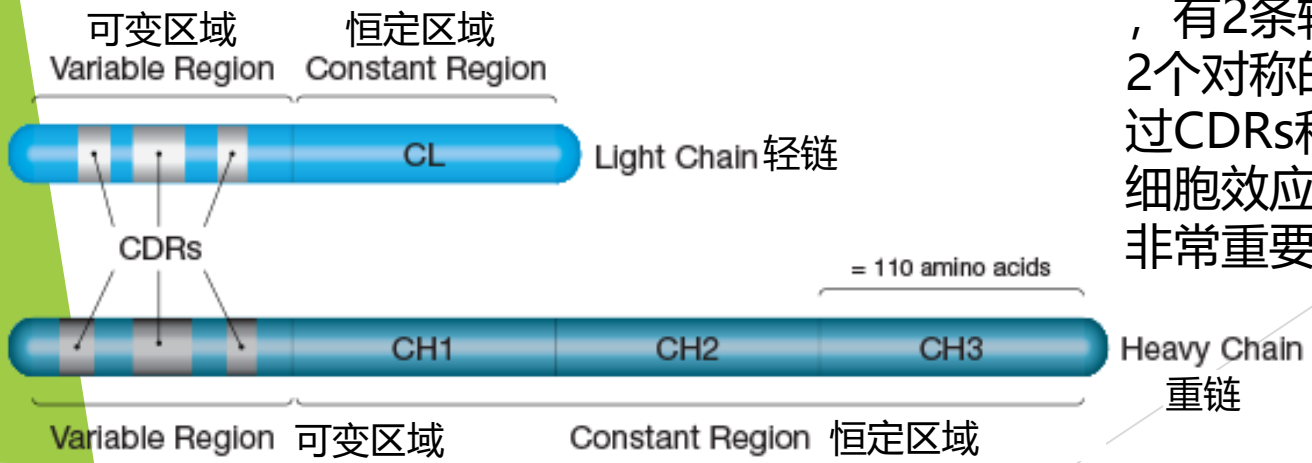
Ribbon结构图



Sphere结构图



抗体的电子显微镜图影

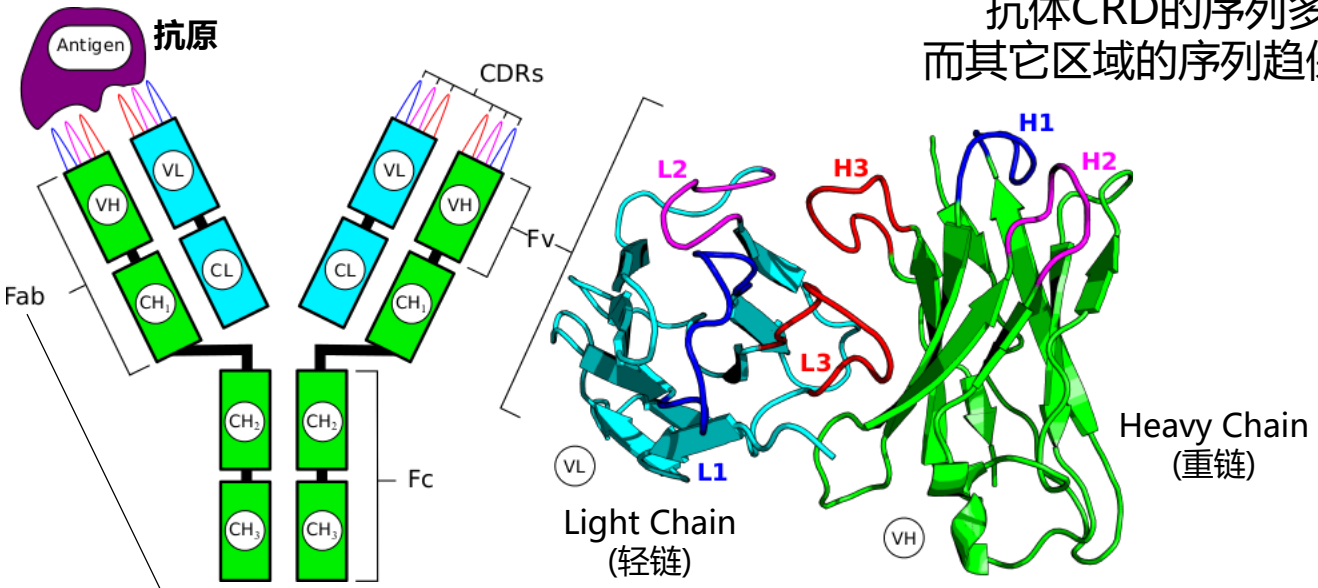


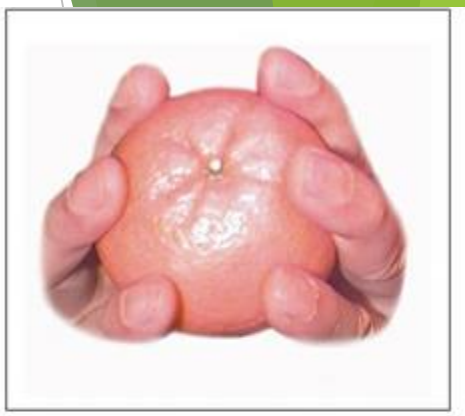
抗体为Y-型结构的糖基化蛋白质，有2条轻链和2条重链组成。抗体有2个对称的抗原结合区（Fab），通过CDRs和抗原结合。Fc区域是引发细胞效应的重要部位，对抗体的功能非常重要。

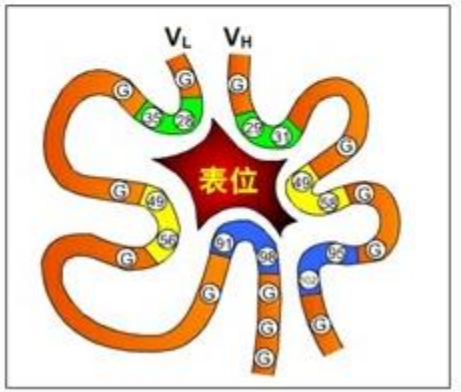
每个成人有40-100g抗体

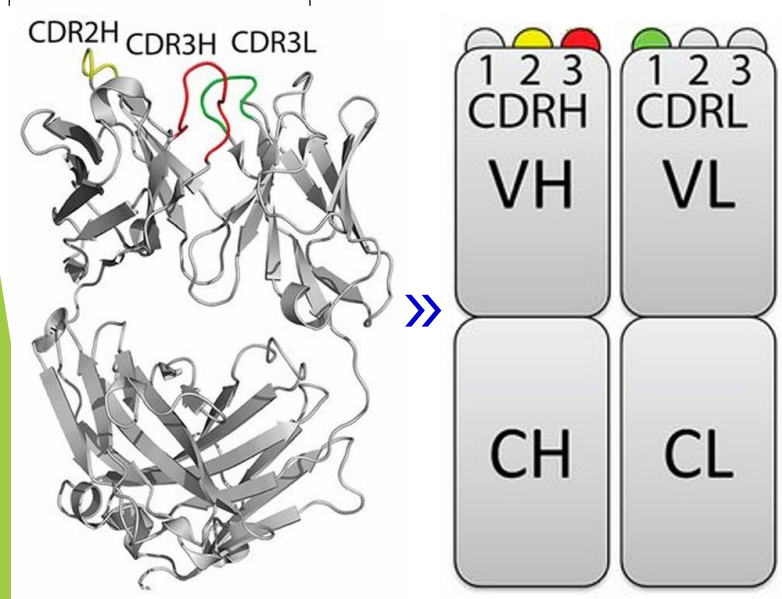
抗体依靠可变区与抗原结合

抗体CRD的序列多变，而其它区域的序列趋保守。

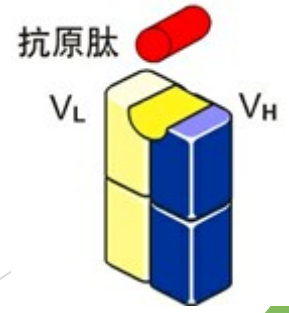


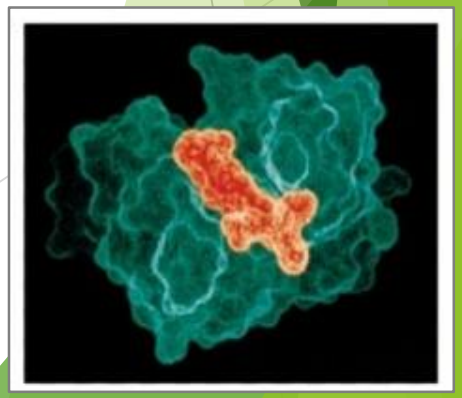






CRD是构成互补位的关键；支架上的其它个别氨基酸也参与抗原结合。CRD和这些氨基酸共同构成互补位。

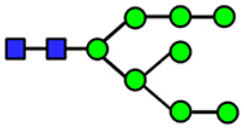


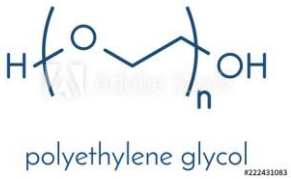


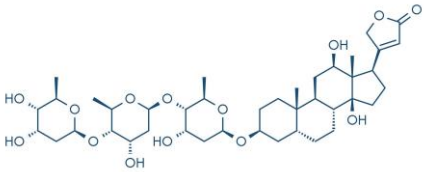
抗体的结合能力和抗原种类

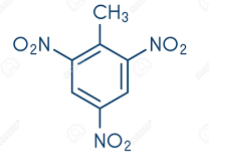
- 抗体对各种抗原分子都具有很好的结合能力

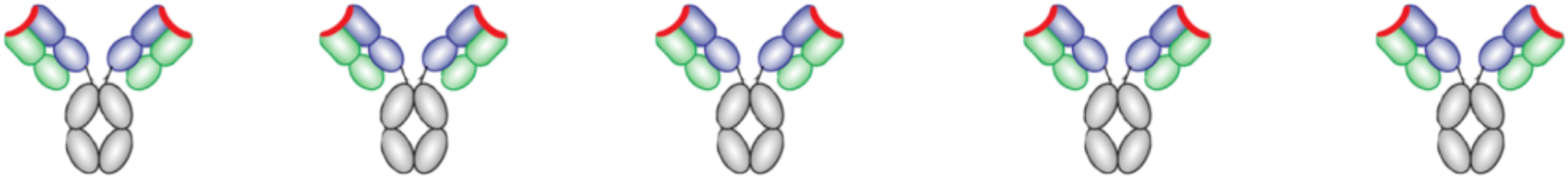
多肽或蛋白　　多糖　　PEG等高分子　　药物　　小分子





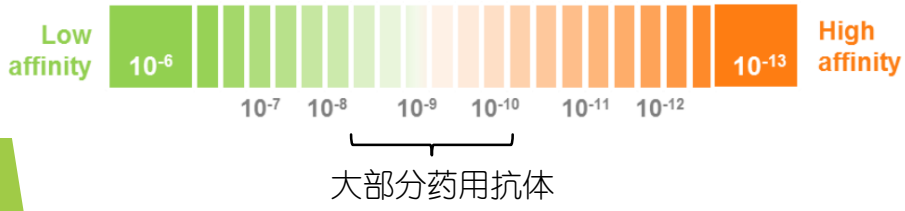




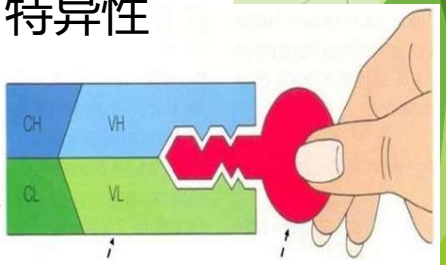


- 抗体的结合能力：亲和力和结合特异性

亲和力，K_D

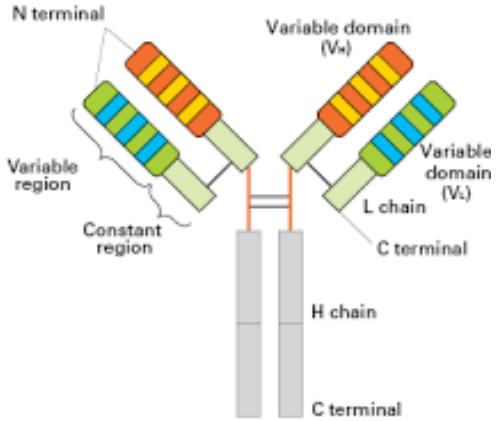


特异性



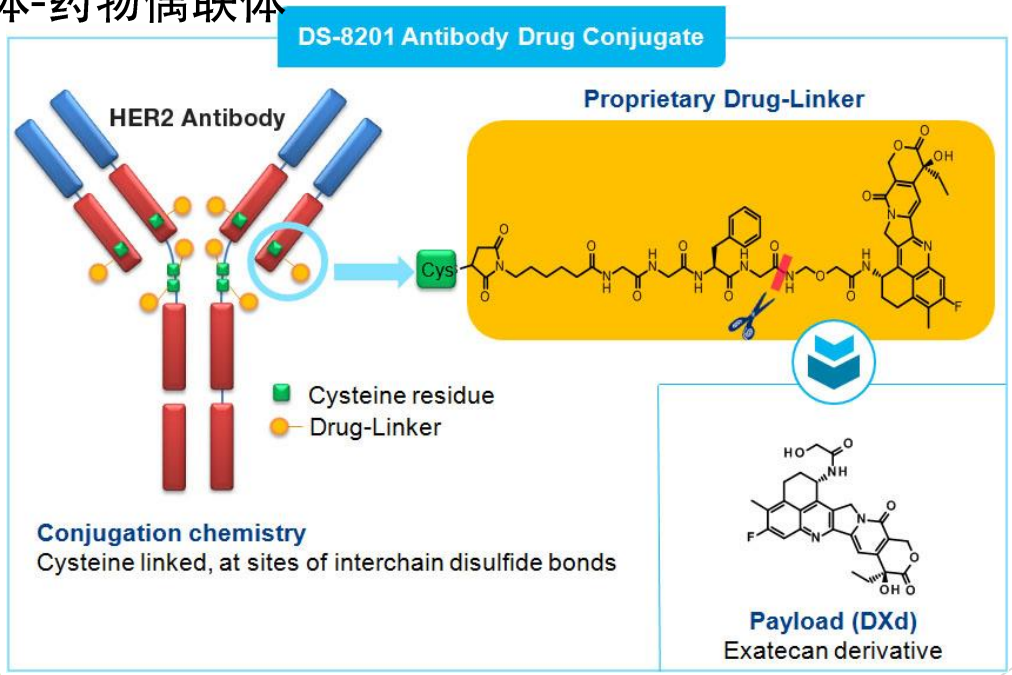
抗体药物的靶向与种类

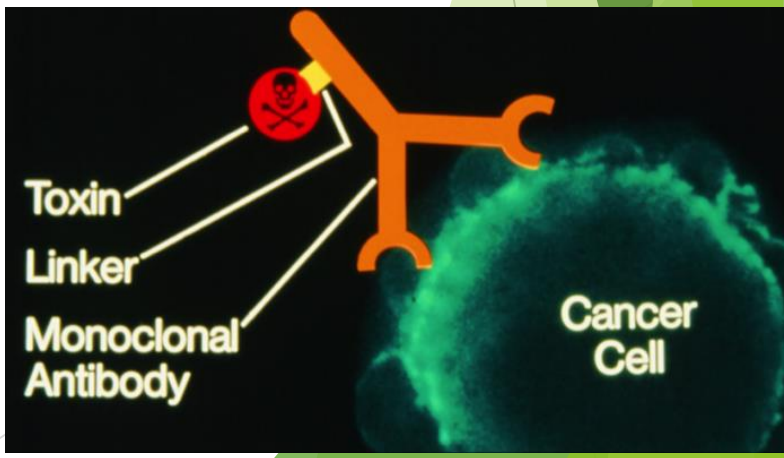
标准抗体



双特异性抗体

抗体-药物偶联体





武汉大学药学院

2022年招收两名硕士生，可直博。需提前进组接受考察，合格者组内提前录取，保研或考研均可。名额有限，邮件联系，欢迎咨询！