we are fortunate to have todays lecture

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of pharmaceutical science at the

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cancer institutes clinical pharmacology

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john earned his doctorate of pharmacy

degree and his phd from utrecht

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yon is an expert in preclinical and

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on mass balance studies

his research interest surrounds the

translational pharmacology of

anticancer drugs and has published over

00 manuscripts and peerreviewed

journals

im confident you will enjoy todays

lecture

hello there i am john burmer

i am an associate professor of

pharmaceutical sciences and medicine at

the university of pittsburgh

i will talk to you about drug absorption

and bioavailability

this is the overview of my talk i will

introduce some pkpd and definitions i

will discuss the physics and physiology

of absorption

focused mostly on oral absorption i will

discuss the biopharmaceutics

classification system

factors affecting oral absorption then i

will discuss flipflop kinetics other

extravascular doses routes and i will

finish up with

bioequivalence

so this is a slide that really shows the

basis of pharmacology on the left you

see the pharmacokinetics what the body

does to the drug and on the right you

see the pharmacodynamics what the drug

does to the body

on the bottom left you see a graph of an

intravenous concentration versus time

profile

there is an instantaneous distribution

followed by a first order elimination

of course when theres an absorption

step involved this changes the

concentration starts at zero and at a

certain rate the drug gets absorbed

presents itself to the systemic

circulation

uh reaches a peak and is then followed

by this elimination phase

on the right hand we see a classical

dose response curve where the exposure

is is expressed as a log value versus

the effect following the emax model

of course weve got to keep in mind that

theres not just one dose response there

are really two dose responses in the

green we see here the desired dose

response curve for the intended effect

and in the red we see the side effect

dose response curve

and the diff the gap in between these

two curves is really the therapeutic

window that we are targeting with our

therapies

another consideration is that there are

likely multiple

red

dose response curves because every side

effect has its own dose response curve

if we now take these two graphs

and put them together

conceptually then we see here in green

the minimally effective concentration in

red the minimum toxic concentration

and as the drug gets absorbed it crosses

the minimum effective concentration and

the effect has an onset it starts it has

a maximum effect the elimination takes

place and when the concentration drops

below the minimum effective

concentration the duration of the effect

has has ended

and this again is the therapeutic window

that we are targeting between the red

and the green and if absorption changes

within a patient between patients we can

reach high concentrations resulting

resulting in toxicity or lower

concentrations resulting in lack of

efficacy

so i just want to present some

definitions of absorption and

bioavailability

what this talk is about these are

definitions from goodman and gilman the

absorption is the movement of a drug

from its site of administration into the

bloodstream or central compartment and

the extent to which this occurs

bioavailability is defined as the

fractional extent that drug reaches its

site of action or a biological fluid and

here you can already sense that these

definitions are not

extremely specific there is sort of uh

a quality to it uh its not its its

the bloodstream the central compartment

the site of of of action uh its its

not very defined

another definition of bioavailability

that i do want to share

is the one in the code of federal

regulations because this is the

definition that the fda uses

its defined as the rate and extent that

an active moiety is absorbed from a drug

product and becomes available at the

site of action

so this bioavailability this fraction

that gets absorbed is really based on

the area under the concentration time

profile

and so here on the right we see the area

under the concentration time profile the

real surface area under this curve when

concentration is plotted linearly

and so one determines this area after

oral administration in green here and

after iv administration the curve in red

and in this case the areas under both

curves are identical and so the fraction

absorbed is one on a log scale this

results in these plots with parallel

terminal elimination phases

if the fraction is less than one

then the oral curve will drop down

correspondingly and you get a lower

exposure

so in formulas this is depicted as as

down here where the area under the

concentration time curve after iv dosing

is the dose divided by the clearance the

dose we can determine by by choosing the

dose and the clearance is a biological

parameter that may differ between

patients

if the dose is given extravascularly

then there is a fraction that gets

absorbed right this this bioavailability

and so that then enters the equation

and f can be isolated as here and so you

can determine experimentally this f

by

ratioing the dosenormalized auc after

extravascular administration divided by

the dosenormalized aoc after iv

administration

next physics and physiology

so here we see for oral administration

the whole path from disintegration of a

solid dosing form to individual

particles in the gut lumen

to dissolution

of individual molecules

diffusion towards the gut wall

through the gut wall

entering into the portal vein

then reaching the liver

and then finally reaching the systemic

circulation

and at any of these steps there is the

potential for loss

as depicted here

now absorption is commonly considered to

take place between the dosing form and

reaching the portal vein

but for oral bioavailability it also

includes this step of getting past the

liver the first time that each drug

molecule has to make it past the liver

and so this is called the first pass the

first pass effect

so just focusing on some of these

processes individually the

disintegration of a solid dosing form is

rate limited by the liquid penetration

into that dosing form

and so drug release will be affected by

a variety of factors the excipients that

are chosen often fillers or compounds

that aid in the processing of the dosing

form

the tablet compression strength is

important for this liquid penetration

and of course any coating or matrix that

is added to the dosing form to affect

these processes

so if you embed the active

pharmaceutical ingredient the api in a

polymer matrix that dissolves or swells

at a slower rate on the drug then this

will

will impact the process of liquid

penetration it also can increase the

disintegration by by swelling up and and

breaking up the solid dosing form

in addition if you coat the tablet you

can create a mass transfer limiting

barrier and so you can create a

prolonged exposure an extended release

form or you can make this barrier

soluble based on ph and so this is how

you can create enteric coated tablets

that do not dissolve in the stomach

juice under acidic condition but do

dissolve once the the dosing form hits

the intestines

the solution is described by the nernst

brunner equation as depicted here the

change of the concentration in a

solution is

is dependent on the diffusion

coefficient the surface area of your

particles diffusion layer thickness

medium volume and solubility

and so if we look at a

the baseline curve the starting point

this black line of a base

bases are usually not very soluble

and so

the solubility is very low and also the

kinetics are very low and so you reach a

solubility

with a very slow pace

if you now take this same chemical

compound the base

uh formulated as the base but you you

decrease the particle size and thereby

increase the surface area that is

available then you will get to the same

final concentration but youll get there

quicker and so this is the difference

between kinetics and dynamics

thermodynamically the solubility hasnt

changed but kinetically you get there

sooner

other ways of impacting the dissolution

process is to formulate a compound as a

salt this increases the solubility so

you get to higher total concentrations

and of course the rate therefore

increases as well

if you note here the change in

concentration this rate is directly

proportional to solubility higher

solubility

you get there quicker as well

in addition you can also formulate

compounds as an amorphous compound

different polymorphisms hydrates

anhydrates etc

and the way you can think about this

that is that if a solid is amorphous

then its not in a stable crystal

structure and so it require requires

less energy for a molecule to leave that

solid form and enter the solution and so

solubility is enhanced

these different dissolution profiles

will then result in different

concentration time profiles inside the

body and that is depicted here

so the next step is to transport these

molecules across the enterocyte membrane

and enter the biological system

and this is depicted here the different

ways that that that can happen passive

diffusion trend cytotic vesicles will

not go into that too much

passive diffusion

in through the paracellular route with

molecules that are hydrophilic and small

facilitated diffusion with carriers

well go into that quite extensively and

active transporters

which include the solute carrier family

and the b binding cassette family well

also discuss these

so passive membrane

diffusion follows ficks first law law

here depicted on the right and so the

flux

is the diffusivity

times the concentration gradient and it

is the concentration gradient across the

membrane so if you then rearrange this

formula what you get is diffusivity

times the difference in concentration at

the beginning

and the end divided by membrane

thickness which would be a constant

now here we have the concentration this

is a yaxis the concentration in the

solution which you reach by the

dissolution process that we just

discussed

and then

in the membrane the concentration jumps

and so this difference is the partition

coefficient of your molecule into the

membrane

and this is kd

the same happens on the other side

theres this ratio of concentrations in

membrane and solution and this again is

the kd

usually one considers this concentration

to be a sink condition so its zero and

so the concentration gradient is

linearly related with the concentration

at the beginning of the membrane which

through the partition coefficient

is linearly related with the solubility

and so if you now combine

this diffusivity the partition

coefficient you get the effective

permeability and this is a parameter

parameter that is often determined with

experiments

and so as you now can imagine the

diffusion through a membrane is very

much dependent on

the partition

coefficient how much does a molecule

like to go into the membranes

and the solubility

now of course

this doesnt

take into account that molecules are not

always in the neutral form only the

neutral form passes membranes

but their drugs are often acids or bases

and so ill discuss this in this slide

this partition

this this this acidbase equilibrium is

described by the henderson

equation depicted here top right

and the ratio of the two forms the

chemical forms that occur is described

here 0 to the power ph minus pka

now i just mentioned that only the

neutral form will pass membranes and as

we see here

for each one

neutral molecule there are a thousand

nions and this is based on the ph in

plasma  and the pka of this compound

the total number of molecules is

depicted here 00

in the gastric acid

with a ph of

this equilibrium is the other way around

for each one molecule of neutral

acid

there are 000 molecules of an ion

and so as you can see here

the equilibrium in the acid is pushed to

the neutral form and on the plasma side

it is taken away from the acid from the

neutral form and so this really favors

absorption through the lipid membrane

now still

weak acids are not absorbed in the

stomach very much this has to do with

the membrane thickness in the stomach

and also the limited

availability of surface area

here we have the same situation for the

base i will not go through it in detail

you can do that yourself but suffice to

say that the ratio is

completely different

its one to a million

and so

weak bases are

very disfavored for absorption from the

stomach understandably so now this is

not necessarily a bad thing because what

it does favor is the solution

dissolution of the compound

as you can see if a molecule

is uh dissolved from its solid form it

immediately gets ionized and so this

drives the equation

equilibrium to dissolution and then once

its all in solution and

these molecules get dumped into the

intestine with a large surface area and

a neutral ph then absorption is favored

at that point

here we can see

a bit of a bigger picture so heres the

intestinal lumen heres the entro site

molecules enter through these these

carriers

they may be effluxed by pgp

and what happens is that they get

repeatedly exposed to sip a

so molecules enter

they may be metabolized and then they

may be pumped back some molecules may

make it past the enterocyte and enter

the portal vein

and here these pumps are no longer in

the same membrane

and in opposite directions once a

molecule is in the portal vein it may be

facilitated into the hepatocyte

again

theres a likelihood of being

metabolized

and even if it doesnt get metabolized

it may be

pumped out into the external environment

through bile and forming the

anthropologic recycling pathway

and so this system is

very nicely set up to prevent

xenobiotics from actually reaching the

systemic circulation

here is a depiction of the entrance site

with the variety of pumps that have been

characterized and i will not go into

this in much detail there are other

lectures that will address this but

suffice to say that drug drug

interactions and polymorphisms uh are uh

are

have been characterized and and are

being discovered uh

every time

so this is the metabolism that takes

place in the enterocyte i just mentioned

sip a and this is indeed 0 of the

phase  metabolism that takes place uh

in the entrance site there are also

phase two metabolic enzymes ugta being

the predominant family

in addition there is gut flora the

bacteria in uh in the gut lumen the

microbiome and these can hydrolyze and

reduce

and change the activity of compounds in

addition this gut flora

has been shown in animals to modulate

the gut and liver activity of sip and

phase ii enzymes and with the

increasing

study of the microbiome this is not a

surprise

so here are some examples

of hydrolysis of lovostatin into its

active compound

inactivation of digoxin

through reduction release of the active

components of sulfasalazine and

prontosal

and this is the reaction of nitrazepam

to its amino group to its amino

metabolite now the intermediate step is

not depicted here but that is a

hydroxylamine and that is a potentially

carcinogenic component

so here i just want to provide another

picture of this interplay of phase  and

phase  metabolism phase  metabolism is

often defined as these carriers and

transporter effects

and so here you see a molecule

repeatedly

being pumped out and

exposed to sip a increasing the

likelihood of metabolic metabolism

and reducing the likelihood of an intact

molecule xenibiatic actually reaching

the systemic circulation

here we show the hepatocyte with all its

pumps and also the biliary

canaliculi

and again

these these hopefully will be discussed

in other lectures

and

there may be drug drug interactions and

polymorphisms that play a role here

so the last step

before a molecule can reach

the systemic circulation

is metabolism in the liver

and so that is a big component of the

oral bioavailability

the total bioavailability is often

split up in the fraction of the dose

absorbed by the intestinal epithelium

the fraction escaping gut metabolism and

entering the portal vein and then this

last factor is the fraction escaping

hepatic first pass extraction and

entering the systemic circulation

so so far i just discussed

very very simplified diagrams but of

course the gi tract is very diverse and

so some of that is depicted here where

the ph changes as you go along the gi

tract and especially the surface area

differs vastly

so the factors impacting absorption are

the surface area vascularity ph fluid

volumes presence of other substances

such as bile

ngi motility and emptying and here on

the right we see

why these small intestines have such a

small surface area there are villi and

microvilli

that really increase the surface area

for absorption

so here i put that in a table and so the

salient details to to look at are that

you know esophagus is not really a place

for absorption the mouth is

potentially

the junum and ilium have a large surface

area

and the rectum and the mouth may

actually avoid the first pass effect the

mouth and part of the rectum blood flow

bypasses the portal vein and so for

example there are oral

tablets that will dissolve within a

minute in the mouth and release its

compound to be taken up very quickly

such as nitroglycerin tablets

now the pumps and the enzymes

that i discussed they are not expressed

to the same extent across the gi tract

and that is depicted here

so physiological factors that cause poor

bioavailability are listed here diseases

of the gut functional integrity

insufficient time for absorption food

effect drug complexation degradation

poor dissolution or permeability

transporter saturation

efflux pump

substrates

gut metabolism and hepatic metabolism

and some of these items i will touch

upon as we go along

another aspect is saturability of

absorption

uh its its one of the points in the

previous slide and here illustrated by

nelotinib so as an alutinib

the daily dose single dose is increased

the exposure as expressed by the auc

over zero to  hours increases pretty

much linearly but starting at about 00

milligram it plateaus out more drug just

doesnt get in

however if you split this

once a day 00 milligram dose in twice a

day 00 milligram the exposure

over that  hours will increase

percent and so a major pk objective in

phase one trials of oral drugs is to

document uh the potential

presence of pk futility if you go up in

those and you dont get more absorption

so now well discuss the

biopharmaceutics classification system

this is a graph

that underlays the development of this

system

and so here we see the human

permeability

over a jejunal membrane

and the fraction absorbed in humans and

as you can see that is a pretty nice

relationship

and so the thought behind the system is

that dissolution

and gi permeability are the fundamental

parameters controlling the rate and

extent of drug absorption

and when in vivo dissolution is rapid in

relation to gastric emptying the rate

and extent of drug absorption is

unlikely to be dependent on drug

solution and or gi transit time

and so we now get this system where

drugs are either high solubility or low

solubility and high or low permeability

resulting in class  and

so how is this defined

solubility

is high if the highest strength of a

drug is soluble in 0 ml

of aqueous media

permeability is measured by the rate of

mass transfer across human intestinal

membranes

or documented in humans

so the purpose of this system

sorry the the bcs classification has

been extended to the biopharmaceutical

drug disposition classification system

bddcs the purpose is to predict drug

disposition and potential interactions

it is based on the same parameters and

the thought behind it is that if a drug

passes membranes easily

then

if it gets filtered by the kidneys

it may easily be reabsorbed from the

renal tubules

if a drug easily

gets

or if a drug gets excreted into the bile

and it passes membranes easily it may

easily reabsorb from the bile

cannuliculi

and so just like i showed the interplay

of pumps and cypa in the entra site

this results in the cycling of a drug

repeatedly

through enterocytes and

sorry through the liver

and predisposes a compound to metabolism

so high permeability compounds are

likely to be cleared metabolically

and so this is how this is expressed

again this is the original bcs

classification system and now apply to

clearance class  and  are easily

metabolized are often metabolized

and class  and class  are usually not

metabolized and excreted by the kidney

or the bile unchanged because they are

low permeable and they will not be

reabsorbed they may be

excreted mostly unchanged

now i will discuss factors affecting

oral absorption in more detail

so food

may impact the rate and extent of

absorption these are some of the reasons

why

food can physically or chemically

interact it slows gastric emptying

prolongs transit time raises ph

increases bile output and motility and

blood flow

it may change the luminal metabolism and

biles bile and lipid components will

inhibit transporters

the effect is of course dependent on the

meal size and composition

another pattern that i would like to

present to you is

the pattern depicted here

and it is the variability of absorption

plotted against the extent of absorption

and so if a drug is extensively absorbed

then the variability is lower and you

can imagine this if a drug is 90

absorbed a couple of percentages more or

less is not going to be a big relative

difference

however if a drug is only absorbed one

or two percent

then one or two percent more or less

is a relative big difference

so

extending the bdcss

classification system to this food

effect fatty meals

so for a class  compound

the extent of absorption doesnt change

much

but because gastric emptying is slowed

the maximum concentration will often be

increased

class ii compounds the extent will go up

these are low soluble

and what happens is compounds are often

solubilized more by food and the bile

bile salts that are released because of

food that are triggered

this will increase the solubility of

these compounds

and the food components will inhibit

efflux pumps and those so this will also

increase the extent of absorption

class iii compounds are often dependent

on

transporters to gain entry into the

enterocyte and these carriers can also

be inhibited by food food components

like bile and lipids and so the extent

is often decreased

class iv compounds are always

complex to predict because all these

effects can have an effect

so heres a pertinent example

of a food effect here we see the average

locative concentration fasted with a low

calorie

low fat breakfast and with a high fat

breakfast and so the food effect on

average is about a factor four

but if you look at individual patients

depicted here some of these patients

have a tenfold increase of abs in

absorption with a high fat breakfast

the idea behind this is that food

generates bile release

kylo microns are formed and this drug

lapatinib very lipophilic dissolves in

the column microns and these are taken

up by the lymph

system and the lymph system bypasses the

portal vein bypasses the liver and the

lymph gets dumped into the superior vena

vena cava so theres no first pass

effect now this is very irrelevant

because lopatinib has a black box

warning

warning for hepatotoxicity and

potentially death and so high

concentrations are potentially dangerous

so currently the patented is uh is is

labeled to be you used fasted at 0

milligram every day and it costs about

seven thousand dollars per month

the food effect is a fourfold increase

and so what is preventing people from

taking a quarter of the dose with a fat

meal

and this has been discussed as the value

meal in the references provided here

additional food effects complexation and

stability six more capital purine is

inactivated by xanthine oxidase

milk has a high level of this enzyme and

the activity of this enzyme is not

diminished by pasteurization or gastric

acid juices

and so this

underpins the interaction there

tetracyclines often complex with metal

ions magnesium iron calcium and so this

prevents absorption of of this class of

antibiotics

and finally fluoroquinolones also

complex with these metal ions but in

addition in addition recent

publications show that absorption of the

fluoroquinolones on protein surface of

milk

actually is a bigger effect than

complexation with these metal ions

so the fda developed the guidance about

food effects

in 00

and all oral products

need to be tested for a food effect

so they stipulated how this would be

designed needs to be sufficiently

powered

it needs to be studied at the highest

dose and the conditions should be such

that you expect the greatest effect on

the gi physiology so even the meal has

been described pretty

clearly

the design in general for the fasted

piece is an overnight fast for at least

0 hours

dosing the highest dose with 0 ml of

water

and no food until four hours post those

and no no water until one hours post

dose the fed component is the same

except that a meal needs to be consumed

within 0 to 0 minutes

prior to the dose

pka parameters that are documented are

listed here and the absence of a food

effect can be concluded if the 90

confidence interval

for the ratio of the population

geometric means between fed and fasted

after log transformation is contained in

the equivalence limits of 0 to

percent for both auc and cmax

and this criterium comes back in the

bioequivalent section of this talk

next i want to discuss the flavonoids

and this is an interesting

landmark paper where the effect of

grapefruit juice

is documented on philodephene pk

so this study documented colon and

intestinal levels of sip and pgp through

biopsies

pka was documented and phyllodopine is

completely absorbed but the

bioavailability is only

indicating that metabolism is a big

component

of the

bioavailability it also studied liver

cipa activity with the erythromycin

breath test

no effect was documented of grapefruit

juice on livercip a activity

ca levels or small intestinal pgp sip

0 or d levels

the effect was really focused on the

small intestinal epithelial ca levels

decrease and this is shown here in

the top right graph there was no change

in ca mrna levels and so this suggests

a direct effect on the protein

a correlation was documented between

enterocytes ca levels before

grapefruit juice and the extent of the

effect of grapefruit and you can imagine

this if a patient has a high level of

sip a

then there is a lot of siba

to

to inactivate by grapefruit juice and so

the change in cmax is that extensive as

well and so here we can see this effect

where with water the philadelphian pk

the exposure is low

together with the first grapefruit juice

intake it goes up and after the th

dose of grapefruit juice its even

higher

and so later on it was shown that

bergamotin and its

dihydroxy metabolite

actually are responsible for

mechanismbased inactivation of ca so

covalent binding of this compound to

ca essentially killing it and

preventing it from functioning further

grapefruit juice flavonoids can also

inhibit pgp and this is documented here

with the caco cell line

caco cells are grown here on a

semipermeable membrane they form a

nice layer and drug is applied on one

side and

permeability to the other side is

documented and so here we see the

control and after addition of grapefruit

juice the permeability increases

and so this was

was concluded to be the result of

pgp inhibition by grapefruit juice

components

so grapefruit juice is not the only

fruit juice that causes interactions

vexophenidine which is a bcs class iii

drug with negligible human metabolism

was studied after water the top curve

percent grapefruit juice so diluted

full strength grapefruit juice orange

juice and apple juice and so all these

juices

quite extensively decrease the

absorption of exophenidine so this is

the opposite effect of what we just saw

with grapefruit juice

and felodipine

and so this is because of inhibition of

the

influx carrier oatp

by components in these juices

so now we have these two opposing

effects

we have an effect on the influx carrier

oatp

and we also have

the

effect on sip a

by grapefruit juice

and so we have here two probes

celerprolol and midazolam

after oral administration

and

this is with the first dose of

grapefruit juice so there is an effect

of celiprolol sorry of grapefruit juice

and here midazolam an effect as well so

both oatp and sipa are impacted

but on day three and day seven we can

see that the effect on oatp

disappears pretty quickly whereas the

impact on ca is more lasting

and so the components in grapefruit

juice that inhibit

oatp

that is reversible

whereas the impact on ca is more

lasting and as we just

have seen from berger motin

from the berger multn slide this is a

covalent interaction and so

ca needs to be resynthesized before

it is back to baseline

heres just an overview of different

compounds different juices different

strengths different

volumes administered

and so

every every substrate and every juice

can have a different extent of effect on

the auc ratio here depicted below

so flavonoid effects depend on which

substrate is studied what flavonoid is

present combinations thereof

concentrations of flavonoids and we have

to remember that these are natural

products right food products and so

location geography of of of growing them

and harvesting time can all have impacts

on the relative levels of these

flavonoids

the western diet contains about 00

milligrams of these flavonoids a day

and some very common ones are listed

here neringine hesperidin the farano

coumarins which includes bergamotin and

the last one i want to discuss is hyper

foreign which occurs in saint johns

worth

hyper foreign is a sip a and pgp

inducer

and when given with imatinib it

decreases the auc nc max of this

anticancer drug

st johnsworth is a herbal remedy for

depression and so you can imagine that

cancer patients may be depressed and

take this as a herbal remedy but in

treating their depression they may

actually compromise their anticancer

therapy

so these transporter effects that we

just discussed they have also been

expressed in the bdcss system

as follows

if you have a class one compound then

there are no transporters needed to get

into the entrance sites

and they enter at such a high rate that

efflux pumps will not have an impact so

transporter effects are minimal

class ii compounds

they will enter

membranes very easily but not to a high

extent because their solubility is low

and so flux pumps may impact that

that absorption process

class iii compounds they dont enter

membranes very easily and so they need

the absorptive transporters and so

interactions at that level are likely

with class  compounds

all transporters could have an impact

and its hard to predict which effect

predominates

next i want to illustrate the effect of

gastric ph

using the satinib the solubility of the

satinip at ph  is  milli milligram

per ml whereas at neutral ph its almost

0 000 times

less and so if you take the satinib

with an h antagonist which increases

the ph of the stomach

then the absorption will be less

and so depending on the tyrosine kinase

inhibitor studied and depending on the

specific antacid used these effects can

exist or not

and for some drugs its not studied very

well and so the impact is unknown

the opposite effect can also happen

acidity can

cause

degradation of a compound such as in the

case of a landronite

and so for this compound the auc

is increased by a factor of two

in the presence of renited infusion

which increases the gastric ph to

approximately neutral levels

here is a an overview of tyrosine kinase

inhibitors and food effects

antacid effects

and what advice is given in the package

insert in the labeling without food with

food

and avoiding antacids or not

next i want to discuss

altered anatomy we shouldnt assume that

patients have an intact gi tract

people have whipple procedures or

gastrectomies because of cancer or

gastric bypass because of obesity

this is an ever increasing percentage of

our population

and these surgeries happen

ever more frequent

this causes reduced gastric volume which

may increase the toxicity of certain

compounds because of a smaller volume

same dose higher concentration

increased ph

changes in gastric emptying and

increased motility

bile salts which are dependent on

entropatic recycling to be taken up and

reused again that process gets

interrupted and can impact the

absorption of certain drugs

and the duodenum gets bypassed and so

reduced surface is available for

absorption

and as you can imagine extended release

formulations in this setting are not

appropriate

so the different surgeries that exist

because there are different types of of

gastric uh or of of

bypasses

they can be either focused on

malabsorption

gastric restriction

combinations thereof

or surgeries that combine male digestion

with malabsorption and gastric resection

the most popular ones at this point in

time are the sleeve gastrectomy and the

roo and y gastric bypass

and heres just an illustration of the

variety

of different surgical techniques that

that have been applied

and here i will illustrate the different

impacts that can have so in this paper

and there are not a lot of good

pharmacology

studies that are that are being done in

this population

but this is an example where theres the

bill roth one procedure the builder of

two procedure and the rule and y

procedure

and so for one drug

here in the dotted line we see the

healthy volunteer control group

and the absorption in all these

these gastric bypass patients has been

decreased but for another drug

the impact is different

earlier tmaxs later tmaxs and so

depend depending on the surgery that has

been performed in the individual patient

and the drug that is being taken

the effect is really hard to predict

this is

two examples from my own lab where we

studied temozolomide pk after roon y

bypass with no apparent change in p k

compared to literature values

and below is a graph of imatinib pk

before

in black

and three times after

sleeve gastrectomy and you see about a

0 reduction in plasma concentrations

and the maintenance of response

for imatinib

to control cml or gist has been related

to trough concentrations and so this is

a clinically very relevant

effect

as you can imagine

industry has been looking to

select chemicals for drug development

based on their bioavailability

and so how can you predict that how can

you select out of your hundreds of

compounds

the molecule that is more most likely

giving you good oral bioavailability

as you can imagine

uh with models in general general the

complexer the model the less it is

suitable for high throughput and so the

complexity of the absorption process

makes it impossible for models to be

relevant and simple

so there are three

items that i want to briefly discuss

first the log p

this is very closely related to the kd

that we discussed in the

membrane diffusion slide

and so this is really the partition

coefficient between octanol and water

for a drug

now why are we using octanol its

because the polarity of oxanal is very

similar to that of membranes of lipid

membranes and so this is a good

approximation that is easily obtained in

vitro

next theres the lipinski rule of  and

the kco cell line system and so these

are

systems that are models that are used by

pharma to select

lead compounds

so the lipinski rule of five is listed

here

basically based on a big data set poor

oral absorption is more likely when

theres more than five hydrogen bond

donors the molecular weight is more than

00 the calculated log p is more than

five too much of a good thing is is not

is is is not great either because then

compounds wont leave the membrane

and more than 0 hydrogen donor

acceptors bond acceptors

exceptions to the rules are often

transporter substrates as you can

imagine

other people have similarly come up with

rules ionization at intestinal ph

particle size stable mole polymorphs

low aqueous solubility molecular

flexibility and polar surface areas

the caico cell line

weve discussed briefly before

this is derived from a human colorectal

carcinoma cell line it is cultivated for

about three weeks and it has

it consists of a polarized monolayer

with a brush border microvilli and tight

junctions

and so you

apply the drug on the top side the

apical side you monitor how much shows

up in the basal lateral side

this is some of the data associated with

the caicos cell line

so here we see the

apparent permeability

these top two graphs plotted against

absorption in humans and so as you can

see the relationship is pretty decent

here we see a different graph where the

caico permeability is plotted against

the human jejunum permeability

that is part of the bcs classification

and again a reasonable correlation

so like any model its not perfect but

it is a tool

the disadvantages are the long

differentiation period the passage

number and inter and intra laboratory

variability the absence of a mucus layer

the absence of a first pass effect

and the fact that paracellular transport

and sip expression is lower in the kco

cell line than in vivo and this has

resulted in the generation of subclones

with different levels of transporters

and enzyme expressions

now i will discuss flipflop kinetics

here we see the process

of dissolution absorption and

elimination

and each of these processes has a rate

constant for simplicity

further i will sort of combine the

dissolution and absorption rate theres

an absorption rate and an elimination

rate

so here in this table there are three

scenarios and in each of these scenarios

there is one rate constant that has the

smallest value and that then is the rate

limiting step

as a rule

absorption rates are often much higher

in value than the elimination rate and

so the elimination rate is rate limiting

but exemptions exist

so here in a graph

we see in green

the common situation

where ka is higher than k elimination

and so we are

accustomed to thinking of the terminal

elimination phase as reflective of the

elimination process

but here

i simulated

a curve in blue where we reversed these

values

and even though the height of this curve

is a little different

the fraction absorbed changes if you

change these parameters

the slope of this terminal phase is

identical

and so what we need to understand is

that the terminal phase

of a concentration time profile is

reflective of the rate limiting step

which not necessarily is the elimination

rate

so how can you find out whether you have

flip flop kinetics where these these

rates are are reversed well you need to

do an iv study and so these are the two

situations

if you dont have flipflop kinetics the

common rule

your iv curve and your oral curve will

have parallel terminal phases the

elimination rate is rate limiting

if they are not parallel then you are

dealing with flipflop kinetics and in

this case

your terminal your apparent terminal

halflife

in your oral curve is reflective of your

absorption rate

and actually the upfront piece that is

your elimination rate

this is a real example from my

laboratory in mice

so here we have the iv concentration

time profile

as a solution of course

the oral concentration time profile

again as a solution

and then we

performed a study orally with a

suspension in one percent carboxymethyl

cellulose

this is a thickening agent to stabilize

the suspension

and what we see here is characteristic

of flipflop kinetics

and so what has happened here

well it turns out that this thickening

agent also reduces the diffusion rate

and so in the gut lumen the drug

reaches the membrane at a much slower

rate

and so the fusion here is determining

this terminal phase it has become the

rate limiting step

this effect can be put to good use this

is not oral absorption this is

absorption from a patch through the skin

and so instead of giving daily doses

with a highly variable concentration

time profile

you can apply one skin patch

where

the release from the patch or the skin

absorption is rate limiting

and so you get this much more prolonged

concentration time profile where your

average concentration is maintained much

longer with one simple

application so your halflife is much

more extended

and this is the rate limiting step from

the skin patch

so there are other routes that are

extravascular than oral oral very

important so thats why i focused on it

but i just want to give this overview so

after iv or arterial dosing there is

complete availability

with extravascular routes this is not

the case

it always involves a rate of absorption

and an extent of absorption

so why do we apply the extravascular

route well often its convenient

and systemic absorption may be desired

its just convenient

in other situations you actually want to

target something locally

the target may be hard to reach

and oh

and systemic absorption may be undesired

because it is associated

with side effects so the other routes

are

for example oral intramuscular

subcutaneous dermal interpersonal

pulmonary infertile ocular and the list

goes on but these are the most common

ones and i want to provide an example of

intraperitoneal dosing

this is from my lab with an ip

regimen for ovarian cancer portezamib

was investigational carboplatin standard

of care and as we can see here in the

two concentration time profiles for

bertazimib

the peritoneal fluid concentrations are

much higher than plasma

same thing for ultrafilterable platinum

considered the active component of

carboplatin therapy peritoneal fluid

concentrations one to two orders of

magnitude higher than in plasma and so

youre avoiding the systemic side

effects which you would get if you dose

these drugs iv you get a much higher

exposure locally where the tumor occurs

in the peritoneal cavity

so lastly i want to discuss the

bioequivalence

bioequivalence is defined by the fda as

the absence of a significant difference

in the rate and extent to which the

active ingredient becomes available at

the site of drug action

these kind of studies are done to

establish a link to

show equivalence of different

formulations

early late clinical trial formulations

clinical trial versus stability

formulations and of course brand and

generic versions the test product is

always the new formulation the reference

product is the prior formulation from

which you have

more data

so these are the situations the test

formulation can have a higher exposure

than the reference

formulation and then the fda would be

concerned and the company would be

concerned about safety if its the other

way around you would worry about

compromising efficacy

and if theres a variability of your

test formulation then you would worry

about both

so in general the study design is such

that you have

these characteristics its very similar

to the food effect study i will not go

through them in detail

and the sampling needs to be such that

you capture the absorption distribution

and elimination phase

you have two samples before the tmax you

document at least three halflives

number of samples and oftentimes you

sample plasma serum or blood

these are the pk parameters that are

documented and the statistics are very

similar to what what weve

seen in the food effect study

so how do we come up with these these

differences that we find relevant this

0 to

interval

well it was considered that 0 or less

of an auc or c max difference is not

clinically significant

and so this 0 results in

a drop to 0 percent and in a log scale

the symmetrical distribution then

results in  as the upper limit

so we express this

90 confidence interval

in the log space of these geometric

means of the test and the reference

formulation and these are four

situations that can occur

if your formulations are equivalent and

you have a reasonable variability your

confidence interval falls completely

within these 90 to 0 to  percent

limits

you can have a

a by equivalence that is not exactly a

hundred percent but if your confidence

interval is really tight it can still

fall within the limits and pass the test

your formulation on average can be

exactly the same but given high

variability the confidence interval can

extend across your limits with high

variability

and so what we can conclude is that

bioequivalence

means therapeutic equivalents

but bio inequivalence like in the bottom

situation does not necessarily mean that

your formulations are therapeutically

inequivalent

if the sponsor has data that the dose

response curve is not too steep

then

these exposure differences with two

formulations may not result in

clinically relevant effects

so the fda guidance does allow for the

waiving of these bioavailability or

bioequivalent studies

if a compound has been shown to be a bcs

class one drug and in that case

formulations can be tested against each

other with the dissolution testing

where a compound passes the test if it

rapidly dissolves from more than

percent within 0 minutes in less than

00 mils of each of these media

and so then you dont have to do a real

in vivo human study

thank you very much for your attention

i hope you found the lecture useful and

if you have any questions please reach

out to the program coordinator thank you