todays presenter is dr ping gao who is

obtained his phd in analytical chemistry

from purdue university

and spent over years in the

pharmaceutical industry

with stents at up john pharmacia pfizer

amgen and abbott

he developed his scientific and

technical expertise in the area of

preformulation formulation science and

drug delivery

please enjoy dr gals lecture

my name is ping gao im working for a

pharmaceutical company called abv

my work is doing

the drug products

development

today it is my good honor to be invited

here to nih to presenting a lecture on

enabling formulation technologies

for improving oral absorption of poly

water soluble drugs

as im working for industry so i really

limited by how many

examples i can really be presenting to

you so im really use the best

literature data plus my own research

work

in the slides and trying to

share with you some fundamental concepts

and also case studies of this enabling

formulation technologies

on this is outline of

my talk first i give you an introduction

second i will talk about what are the

enabling formulation technologies which

i really listed here in four categories

below

one was the project one was the

nanoparticles technology another lipid

formulation technology

the last one

is the muffler solid dispersions

then we are trying to give you

a general overview the mechanistic

understanding

of the improved absorption with this

formulation technologies

and our withdrawal conclusions at end

first

were really working on the drug we call

the api epi called active pharmaceutical

ingredient thats basically common name

is a drug youre starting with a drug as

a powder

really you give the patient is is the

oral drug products its easily

presentable

in the pills or capsules tablets or

sachet

but they need to be formulated

formulated means you really have

converting the drug powder

to be um adding

other excipients

that would be

at the drug products it must be

bioavailable

and also stable means chemical physical

stable and also manufacturable

so how do we really make the api goes

into the autodrop product this is called

a formulation

when you really have drug products

really take orally into your gi tract

the drug product will go through

multiple process which is kind of

pictured here

first you go to your stomach you really

could have a

disintegration of the drug products in

the stomach which really become

break down into particles powders

then really

the powders will be goes the gi fluid

goes small intestine

the major absorption

would happen in the small intestine

glucomembrane

before you really get to the

absorption part the drug powder has to

be dissolved in the solution that means

the drug really has to be in the

solution so the dissolution is one of

the first important step

the second one really the solution

[Music]

touch the membrane the drug part the

drug molecule would pass through the

membrane in order to get really absorbed

so this is the

kind of twostep process which is

outlined here

the first step you have to really draw

particles will be dissolving into

solution

reach the concentration in the lumen the

cl means the drug concentration in in

the lumen

the seconds there if the drug really

have to touch the membrane goes

penetrating or permeates through the

membrane through the portal vein which

is good to systemic circulation

the first is the solution the second is

permission

and two major steps are considered the

most important

factors in

the drug absorption process

theres a multiple

those reforms first we call it immediate

release which is indicated here as a

very fast

high cmax which

quickly declined another drug products

type called extend release which would

reach a high concentration but not the

highest youre trying to control

the concentration in the body by control

the release rate so these two very

different type one called immediate

release one called extend

release

and which is a lot of time based on the

therapeutic activity we want to be

either ir or er

so in this lecture

we only talk about immediate release

because most of enabling technology can

be used for extend release but the

majority work which im talking about

today

are really within the ir type

as

as i just mentioned that we have a two

major

uh steps one is the dissolution one is

the permission this two part actually

relates to the major attributes of the

drug products we call a solubility and

permeability

so this is the bcs scheme which is then

of a biopharmaceutical classification

system pcs

was proposed back to 99 now is very

well

adopted by the fda which is as a general

guidance

on the bcs one and three this category

was a high solubility

that means you have really could

dissolve in the drug which is less than

0 this line here is about 0 ml so

you really can dissolve the total dose

of the drug within a 0 meals of water

you have high

solubility

with high solubility you could have a

high permeability thats a bcs type one

you could have a low

a permeability is called the pcl type

three

on this category we consider

the solubility is good enough

but really depending on how the drug

really uh be

penetrating or

or permeable to the membrane

on the right hand is

with a low solubility with a high uh

and permeability or low

permeability so this bcs and the

drugs which are most times considered a

very challenge for instance with the

bcs drug

even the drug is

highly

impermeable but its solubility is low

which means not really being able to

dissolve in the gi tract which is really

require a large volume of water

in the system which we dont have

so this is on the bcs and the four

drugs you really need using enabling

technology in order to deliver the drug

the bcs

system

has really been

become a very major concept to driving

our

drug

products design

and

and

develop process

this simplified the drug absorption by

two primary factors thats promoting

understanding of the key

biopharmaceutical

and properties

which is most important with guiding

selection

of new chemical energy nc stands for new

chemical

entity with a meaningful criteria

and expectations

for how would you try to

understanding what are the challenges

really facing

for a new drug

products

and also really helping us to improve

the efficiency with focus on overcome

the major challenges

and it is very widely used by regular

guidance by fda or by the european ema

which is for clinical studies and by

waivers

before we talk about the detail id like

to give you a general understanding how

is the challenge

major for

the oral products for bcs two and four

compounds is the high dose number

the dose number is defined here is the

dose of the total amount of drug

divided by 0 ml why 00

0 mil it is a little arbitrary it is

considered is the most commonly

used volume in the gi fluid so even this

is arbitrary number it has been very

widely used for this concept

so the dose divided by 0 ml

thats kind of concentration divided by

c star c star is the drug solution in

the medium

if the dose number is very high for

instance

beyond 0 or 00 we know that those

number really could presenting a big

challenge

the second concept here

we call the maximum absorbable dose

which is

really treating our gi tract as a pipe

you really

have

the drug concentration which is

necessary in order to get the maximum

amount of drug really get absorbed so

lets say you have a solubility cs is

this here the microgram per mil

if we give a dose

about 0

milligram

even with the highest pe

you could really get all absorbed up to

five percent

if it really goes to solubilities again

0 microgram per meal it could boost by

the factor of 0

if you really goes to 0 microgram per

mil you can read almost to 0 to 00

you really have the high solubility here

so you can really get

completely absorbed so the concept here

is you really have to working on the

solubility in order to get

the high the complete

absorption of the drug but we normally

we dont have a high solubility

so the key concept of the enabling

formulations

can we generate

a temporary supersaturated state means

the solubility

of the drug

it is one microgram

per meal but can we

using any technology to make the drug

really reach about 0 0

even 0 microgram per meal

then we could really sustain it for a

short period of time which on hours we

dont need a days or months we only need

every hour two hours even its slightly

longer

then we could really

boost the oral absorption so this is the

one of the key concept im going to

refrain back and forth multiple times

lets back to the dissolution rate

the dissolution is the first step which

really require the drug to be absorbed

the dissolution rate here is

well

described by by the

noise a whitney

equation

the dm dt is the dissolution rate

proportional

the d is the division

a coefficient actually is the diffusion

a thickness this is

fixed

however the particle surface error a

the cs is the concentration of the drug

near the surface the cb is the bulk

the a

cscb

variables

so

the key objective here if we really want

to enhance dmdt

we could really enhance the surface area

as many the particle size reduction

we could really using surfactant to to

solarize the drug to increase both cs

and cb

we could also use a muffler solid

dispersion technology to increase both

cseb

we could also use the project so this

all the technology are very much based

on

to change the three

variables a

cs and cb

so now im going to talk about enabling

formation technology in four

categories

first lets talk about pro drug the per

drug essentially is

a parallel drug attached a chemical

a chemical

function group which change either

solubility

or

the absorption rate

so really you have the moisture which is

really attached to the parent drug

but this

the the the moiety has to be

off in the either in the gi tract before

or after

so this is the drug with

attach the new functional group

we call a new chemical entity

will be more in the in

in the biological

environment really

back to

chemical or biochemical process because

the transformation

really

the parent drug

separate

this is a wellknown case for

hiv

drug with eight for eight

this is the

parallel drug which is have a very low

solubility was about a microgram per

meal

with attaching the chemical

function group with the phosphate

related function group

really increased the aqueous solubility

about eight times high

and this really has been marketed as a

product

in the market which is as from gsk and

this is giving much better chemical

stability and also as a bio availability

this table

are really from very recent

review articles

talking about

the

products approved by fda since 00

the product approach has been very

widely approached

used for either enhanced solubility as

it were enhanced the target delivery and

to to improve the

affirmation and so forth

so per drug has been very much widely

used to fundamentally alter

the drugs physical chemical or

biopharmaceutical

properties

to

make the drug up better for

human use

now im changing the gear to talk about

the nanoparticles the nanoparticles is

based on very simple concept we give

amount solid

you really break down to pieces when you

break down the pieces this

becomes very small particles

they present a large surface area

heres a very

simple

mathematics

uh

analysis lets say take a cubic the

cubic which is with the fixed dimensions

we change the political side smaller you

can really change the surface area the

surface area will be proportional to the

particle size is the smaller the larger

particle size

the smaller the particle size the larger

the the surface area

when you really have a large

surface area the the dissolution rate

will be different

here you talk about the particle size

which is with given the solubility if

you have a

large particle size with 0 microns it

take

minutes

if you really go down to solubilities

low to microgram

per ml with one micron particle size it

takes 0 minutes if it goes down to low

solubility as tens microgram per mil

even as one micron take about two hours

we know that human gi trancing time is

very short only limited three to four

hours

so the dissolution rate here

are very important factor if you you

have to reduce the particle size when

you have a low solubility compound

because you want to really shorten

the dissolution time

only here you look at this particle size

when you reach a low solubility

you have to be in a nanoparticle size

range in order to within

0 minutes to a few minutes time window

in order to get the drugs really

dissolved in the gi tract and get it

really get drug

absorbed

so this is the study from merck theyre

talking about

one of the drugs really

reduce the particles giving the drug in

a solid suspension

with different particle size

you can see

the pk profile of a fundamentally

changing

from a

micron particle size will be

increased the pk profile when the

particle side reduce the microns

further reduce the 0

you can see the pq purified get much

better

get a high cmax get more complete

absorption

due to the particle size

reduction

when you have the particle side

reduction youre also facing a two

different

scenario

the first

scenario is the caller dissolution rate

unlimited

and here you see when the particle size

youre starting with 00 microns go down

to 0 0 down to 0

the

the fraction of the dose absorbed really

changing

as you reduce the particle size and this

analysis is done by dr yi

which is published in 999 this is very

well proved by the our clinical

practice

but when you really have another case

which is that have a very high dose

number which i just mentioned that that

when i have a high dose number here

the particle size reduction um of

the the improvement are very limited

heres a demonstration has

different doses

the red dose is 0

the green dose green curve represents a

00 and a thousand so you can see these

three

curves which indicates no matter how you

do with the high stove

the fraction absorbed will be limited

no matter how you reduce the particle

size

so the particle size

reduction

it really could be very limited we have

high dose number so we use the enabling

technology

this is the one other factor we have to

take into

consideration

the tricore is one of the

products

in the market which utilize the

nanoparticle technology

this drug is a phenotherate its a bcs

compounds if youre looking for the dose

number its about

which is actually

very interesting case here

the rule of thumb is if those number is

less than 0 you may be still it be able

to use a nano

particle technology if those number is

really beyond 0 the technology probably

will be considered are not very

useful

this is the the clinical data in humans

which is indicate

with the original

nonnanoparticles which is typical

the phenol vibrate capsule on the market

with a radical

you not have a complete absorption

when you have a

nanoparticles based tablets you can see

the boost of

cmax and aucs you have much better

bio

availability

on on the left hand on the right hand

here is indicates

when the dose form when the dose reform

given is the fat or fast state

almost the same aoc the food does not

have an impact upon

the drug absorption thats a good sign

this means patient you dont have to

take food when youre taking this drug

products

if you use back the old patient

old capsule the patient has to be really

being take care

taking the the product with the food in

order to get a maximum absorption

so when you use the nano technology we

really promote a complete absorption of

drug

which means you also really you dont

have to worry about the food effect

here ill try to give you a general

summary how the application of

nanoparticles technology

which is certainly you can use for

improve the rate of

absorption would you change the cmax

shorten the tmax

it could really improve the extent of

absorption which basically is a high auc

and this has been very early on used

because the nanoparticle can easily work

in the laboratory so it can be

more broadly used for tox studies in

early discovery phase

on the drug products can be used a

parental in

in other

pulmonary so force

this is the table i selected

listed

five commercial products using the nano

technology for oral

applications

this is the if you look at it here

theyre looking for these drugs are

really

basically have high log p

they have

um the

dose are

not necessarily too high so lets

make the drug products within a

reasonable dose number which is can be

used

the nano

technology

now im changing the gear to talk about

lipidbased

formulations

the lipidbased deformation which is

very much based on the old concept you

have to use a surfactant surfactant is

molecule you could have a hydrophilic a

hypothetic balance which is here b which

is means

the surfactant where forming the mild

cells in aqueous environment especially

with the high hiv

surfactant

and this surfactant will be

solarized the lipids

to forming the oil in water

emotions in our

body we normally only forming this is

with the surfactant

on this category in order to get drugs

really sulfurized

the lipids if commonly like we taken

eating oil then the the the

audio so forth theyll have a low hlb so

this is really not very good so

surfactant is a very important part

in the lipids based

formulation

a lot of times our body will generally

buy salt which im talking a little bit

just later the buy salt actually is a

very effective surfactant which can

supervise the lipids and also forming

the

bio acid mixed mice cell which is solved

by the drug which can really be helping

deliver the drug

one of the key important factors talking

about here is the critical micelle

concentration

cmc this effect has been used in

the such amount to generate to to

surpass

the cmc in order to be forming the

micelle

the drug in this case the green

particles will be solubilized in the my

cell in this case we called

cerberization so the drug concentration

can be

increased because the

drug partitioned into the micelle

lipid

formulation

you have to have almost the full

component the first one is a solid

normally you dont have much choice for

human use one is ethanol problem glycol

peg glycol

glycerol so force

as i said we have to use high hvrb

surfactant which

such as commonly used tuning vitamin

tpgs equipment fossil force

lipid you could have a variety of

different lipids which called a fatty

acid or you could really have

a glycerite

which you have

depending on the

fatty acid chain lens

you could have a variety of different

lipids

however

when you have lipids you typically use

have to be combination with the

surfactant and also with adding

solvent

in order to really make the drug

products really be emulsified which is

which you indicate here

this

cartoon indicates

the softer gel

containing the drug solvent lipid

surfactant

and really can be released in a gi tract

in the water and forming a micro emotion

or emotion

in this case we most time we design a

drug which is tend to be selfemulsified

i mean you dont need a lot of agitation

the drug really

the formulation

when the encounter with the gi in water

it becomes emotion or micro motion

droplets

and this is you dont have a dissolution

barrier so this could be very rapid and

mixing

with the water in the gi flute

and the lipidness effect may undergo the

lipolysis in the gi tract which could

also affecting

the physical

state of the emotions which im going to

touch a little bit on in in my lecture

here

depending on the formulation concept you

could really could have the completed

civilizational drug

that means you dont want any drug

be having a super saturated gi

such as good case here is the nero

im going to talk a little more on this

case

or you could have

intentionally to design the drug

products

to forming a superstatic state

in this case you need adding polymer

which indicated here

you need adding polymer

trying to helping the drug

kept in the superstatic state the

concept going to to be discussed in the

next few slides

lets first talk about neural cycle

spawn cycle spawn is a very well

utilized old drug which is being used in

orgo transplant so forth

and youre looking for the structure is

on the peptide structure

have a low solubility

and

theres two commercial drug products in

the market

the older one back to 990

is called saint domingue

i think the new law was introduced in

99

which is have a

much different formulation in terms of

content of the

of the lipids

here i listed all the

the component here which is

you can see

the difference on the lipid here is the

surfactant and lipids

does mainly actually

generate a very different emotion in the

sentiment you generate a coarse motion

causing mutation in the particle size

about two micron to five microns

with the neurogenic the micro motion

which is certainly

much smaller about 0 nanometers

and also because though use the lipid

difference they have a different

dispersion they also have a very

different response in the gi tract

look at here is the clinical study

results

this is the

sentiment

the auc divided by dose

sentiment was the neural

on different dose

the neural

consistent issuing almost twofold

better

auc

so this is really means

the neural formulation are better

bile available

if youre looking for the food effect

the sediment have a significant food

effect the nero have much less

so that means patient you dont have to

take the drug with the food with neuron

this is probably the most important part

with the difference with the sentiment

the euc or the bile availability of the

drug very much depending on the

secretion of the bioasset in the gi

tract this is really clean study you

have the t tube open

which is

bypass the biosol

the patients arms have no absorption

so that means for the organ transplant

patient

if you dont have the bio salt secretion

you really cannot really make the drug

really functional

in contrast the nero has

almost independent

performance it doesnt doesnt matter

you have a bio salt press or not

this makes the

the nero are far better

products than sentiment

a list here are multiple lipidbased

formulations on products

this is

from different companies for different

indications

these are really

uh well

marketed drug products and look at log d

essentially

beyond three to five

so this is typically used for very

hydrophobic drug products

now im talking about another case which

is called

the drug

can be really kept a super saturated

state in order to really get the drug

really absorbed the better

the cytococc still on the market which

is uh

for the

very important pain relief

when really used for marketing products

the capsule containing a crystalline

drug which is generally the low cmax

which is not really very good for pain

relief

they also have significant food effects

that means you really want to take food

in order to boost

the bio

availability

so that time we are trying to work on

to demonstrate to to really investigate

how can we really trying to create a

drug product with a high cmax which is

really

needed for pain relief

this is the first concept study was

really designed to drug products and

were using in vitro tests as well in

vivo docs

in we were studying docs trying to

understanding how the

drug

performance

this is the same formulation with the

polymer which is four percent hpmc this

is the same formulation without a

polymer

they have a very different concentration

profile upon in vitro

a release profile

the red curve here means we have a four

percent hpmc the drugs tend to be stable

in the solution

and also presentable for long hours

about six hours

and this trend this translated into dark

studies the radical

with the black curve you have a

significant difference this is almost

three times better on the auc and the

cmax

and the reason is because

we use the polymer here try to kept the

drug

in the supersaturated state and this

drug really can quickly

absorb

that

demonstrate

the supersaturated state is one of the

primary factors can enhance the drug

absorption

and this is the clinical data in humans

and the black

profile here is really use the

commercial current commercial capsules

which use as comparison

this is the

the blue curve is use the

suspension

the suspension particle size starting

with nano then then so you can see

slightly high cmax

but overall the euc are comparable to

the commercial drug products

look at the red curve

the record is a softer gel which

containing the super saturable

selfemulsified drug

delivery systems

which you really you have

threefold cmax

and twofold auc compared with the

commercial

capsule

this is really indicate you have a rapid

and complete absorption of static cox

when youre using the right

technology

now im talking about amorphous solid

dispersion

warping

amorphous

we know the drug really most time we

have the drug in a crystalline state

the things are really arranged in a

crystalline lattice

the drug products are really have a high

crystal lattice energy the drawer really

have a fixed melting point

if the molecule really are disorder

i mean they dont they dont have a long

range threedimensional

molecular arrangement

so there

are

no such a melting point and the drugs

really are very much randomly

combined

forming called amorphous solid

they are

behave almost like a liquid

so this is they dont have a high

crystal energy so their dissolution rate

will be much

improved so this is the cartoon we

indicate

we put the drug mixed with

the carrier which typically is the

polynomial

and really making a solid dispersion

which is trying to as a

api

the concept was very much discussed back

to 009 which indicate

can we really

change the drug solubility and in the gi

to reach to high enough

then because the

because of the supersaturated state its

not really a stable state its

metastable so the drug really

essentially forming uh

like spring

put the drug concentration high enough

and gradually decrease it caught a

a parachute so its landed on

uh here give a definition of degree of

supersaturation is the concentration

difference

between the concentrationrich level

with increasing drug solubility

so the difference really here

c

divided by s interesting is called

apparent degree of

supersaturation

if you read it for

very scientifically

definition

this should be really free drug

concentration

minus the increasing solubility

then divided by the solubility so this

is really almost a product approximate

definition for the e to follow

we know that the drug retention

have a strong tendency to crystallize

so theyre reaching a critical

nucleation concentration

theyre going to crystallize as a

solid

we

it is very difficult to measure the

critical nuclear concentration which is

cnc

but we can really try to

using experimental approach try to

determine at what kind of concentration

theyre going to

crystallize

fortunately we find out

this critical new nuclear concentration

its not a constant

you can really changing the critical new

country

change the cnc

by adding polymers

the polynomials really

interfere

with the nucleation process

which is really being slowed down

already or preventing the drug

precipitate as a solid

this is the four

polymers we commonly used

one of the first one the pvp

another one is called a copovator these

are pretty much

hydrophilic polymers

we could also have hpmc and hpmcas

theyre a little more hydrophobic

polymers and these polymers are very

commonly utilized in the drug products

with a solid amorphous solid dispersion

nowadays

theres a different

manufactured paths

the commonly utilized are the two type

when we call the spree dry

the drug and the polymer dissolved in

organic solvent you really speed dry

making a powder they use a powder

to be a starting

material

another one called use the thermal

extrusion process you can mix the drug

polymer and really goes the extrusion

process really become danced

substance

you could have generated

the

drug polymer in three different states

the ideal state is that we call it a

solid solution

which is stable

the drugs really completely molecularly

mixed with the polymer and forming a

very stable

system

another you could have a morphous drug

really

more as the clusters

in this matrix which is not very good

which is called metastable

the last one which is undesired is the

crystalline drug in the measure you

cannot really make the drug really we do

have the circumstance like this this is

almost tell us this is not really a good

system so you really you have to be

really trying to identify

what youre generating with a solid

state ideal case you general molecular

level solid solution in order to use the

amount for solid dispersion

im going to discuss the case here which

is with every drug products

we have the

this is for the aids patient the first

drug is called a uh

lutonomy which you see the high dose

number here is 0

and with normally the autonomy is a pcap

booster this really be used for

promoting the other drugs

called a leuprenovir for

for its the medical

treatment

autonomy is a free base which is using a

highly ph sensitive solubility

with crystalline drug you see in the low

ph

you have a solubility is very low about

0 microgram per mil

but with radiomorphous

drug you can really reach a full

milligram per ml

on the right

figure demonstrated a very different

increasing dissolution rate which is

about 0 times better which is

corresponding to this enhancement of the

solubility

improvement

so by using a mufflers drug

you can really enhance

the dissolution rate because the

solubility

increased

this is a study we did in the docs which

demonstrate

asd stands for amorphous solid

dispersion

if you use ten percent asd with twenty

thirty percent you see much better

performance than the physical questing

mixture which is ten percent pb with the

pb stand for physical uh

a mixture

and indicates

that how the bio performance is very

much sensitive the drug loading so 0 of

the

drug loading give the best

performance

this is consistent with our

understanding we have a more hydrophobic

drug content in the asd you tend to

decrease the dissolution rate this is

the part of the reason

this is the

commercial products its called a cliche

it is uh combining the two drugs which

just talk about it glutanova and

lupenovir

this is manufactured through the

homomedic tuition process

and both the drugs are present in

muffled state

and with this drug we replaced original

market capsules

to reduce the three capsules

by two tablets

we demonstrated new food effects thats

very important

and also we have a room temperature

storage that the patient can carry all

the time so this is really enhance the

patient compliance and very good

products you can

carry on you dont have to take the food

so this is a

much better product for each patient

im going to talk on another case which

is a research case

this apt0

is

a drug which used for hcv kennedy we

test

and clinical

because the cleaning core

efficacy so the drug was not really

advanced to drug products but all the

studies done here are used to human

for prover concept if youre looking at

the

drug have a very high log d

of three and have a

two pks which is

highly ph sensitive the solubility is

highly ph

sensitive

in a gi lumen if you look at ph seven

below the basically solubility is

constant less than 00 microgram

per meal

but those projectors 00 to 00

milligram

give a very high dose number so this

means we know

its a very highly challenged drug

we need to work on for oral

this is the clinical study results which

give you a four different

formulations the first one we call the

amorphous solid dispersion tablets using

the polymer called the cupolum

the

wg stands for wet coordination

process

aec tablets means the two different

composition theyre slightly different

in their

compositions

the capsule which is basically is a

crystalline drug mixed with other

excipients which is used for clinical

studies which have low

low dose

so their relative bioavailability was

listed in from clinical studies

the asd gives the highest

which

normalized by the dose

the regulation tablet

gives about a 0 percent the capsule

only gave us

so this

study in in which you demonstrate

how important

is the supersaturation

if youre looking for the capsule the

black curve

essentially is essentially on the bottom

of very low concentration by our

individual test

the

wgwc which is in the shortlived

shortlived

concentration and quickly go down

means the drug release reach a high

degree of supersatisty then collapse

that decline back to

the low

concentration

only

the blue curve here which is reached a

high concentration and lasts about two

hours

and this is really due to the

supersaturation of the drug with kept in

the solution

because we use the right occipitans

and this indicates

the amount of the polynomial used with

the drug in asd

the drug polynomial ratio is

in a wet grenadian

use much less polymer and capsule is the

no polynomial

so this is really indicates if we use

the right of drug polynomial ratio you

can kept the drug

you can keep the drug and the gi

content contained high enough in order

to boost

their

bio availability

this is the

commercial esd drug products

kernel available on the market

if youre looking for their log d a

typically

three and two five

and those numbers high

you can look at the dose

so this is very much reflecting the asd

technology are very much effectively

used for

hydrophobic

drug

molecules

finally i touch about the mechanistic

understanding of improved absorption

what is the polymer doing try to to keep

the drug in a superstitious state

so when really drug polymer are in the

homogeneous solution

without a polymer

the drug tend to be

crystallized in the christine

nuclear which is forming a crystalline

lattice

so if you dont have polymer there so

that this pathway is very much naturally

goes to from supersaturated state

crystallized become a christian drug and

back to very low solubility

we have a polymer here we call the

polypolymer crystallization inhibitor

which is called the pci

you really can preventing the past go

through you only can goes to amorphous

because you have a polymer

absorbed on the nuclear surface

really trying to

interfere with the crystallization

process so the drug products cannot be

really forming a crystalline but forming

amorphous solid

the the muffler solids become aggregates

together

so you can really effectively try to

using the polymer

type or the right amount

relative the drug try to control the

crystallization process

in level so this is the most important

concept

truly

not necessarily with a marvelous solid

dispersion and also with the lipids

based they also can use for product too

so so this is the very most important

understanding how the polymer be very

effectively trying to changing

the crystallization process in vevo

this cartons tells what happened in

vehicle absorption

we typically have a three pass

for oral

if you dont have interference this

motor drug dissolving forming a free

drug get absorbed

with the lipid you could really have

surfactant

you really forming emotions and goods

lipolysis and get absorbed

our nature body

secrete

by salt and were forming a bio acid

mixed micellar bamm stands for biased

and makes my cell

this really can sort by the drug

we normally have a food effect

because this pathway

so if we really we want manipulate the

different contributions

we want to minimize the food effect we

have to maximize

the the two pathways

the supersaturation is a very highlight

here is youre trying to raise the drug

concentration the freeze drug contention

high enough you really make the drug go

through

this pathway supersection pathway if we

went with the lipids based you really

have to use the drug forming the right

lipids

surfactant because lipolysis

so these two paths we im highlighting

here

are most commonly used

for the

amorphous solid dispersion or lipid

and those reforms

by understanding the absorption pathways

which can be really guiding us

how do we choose the right

functional excipients and how do we

really control the drug release rate so

forth in order to really get the best

drug products

finally id like to conclude in my talk

we talked about how do we select

and this enabling technology we talk as

at least the four different enabling

technologies

how we make our decision

the most important we have to look at

our drug molecule and were really

looking for the

the molecular properties physical

chemical properties

here

im using a very

simple

parameter

tmtg this is basically looking for

representing

the driving force for crystallization

an x

on x

axis are using log p

as indicator

for log p typically less than two and a

half

we call them conventional technology

means the drug is not too hydrophobic

you can really use conventional such as

crystalline drug mixed with the

functional recipients you dont have to

really use enabling

technology

only when the drug gets very hydrophobic

which typically lock p beyond two and a

half

dont treat this line uh uh a very rigid

line this is sort of very much effective

lines we really have the high log p you

could use pro drugs commonly utilized

for all kind of hydrophobic drug you can

use for nanoparticles you can use it for

muscle solid dispersion you can use all

different categories

but the nanoparticles typically used

only for high melting point and which

you cannot really use the

amorphous amorphous solid

dispersion commonly utilized a very wide

range but with too high log p

you have to really go to lipid because

it tends to be lipidal really could

really try to enhance

the absorption

which is the muffler solid

this version cannot

further understanding the chart probably

really require a lot of

scientific understanding

why

this technology has certain

limitations

this slide ill give you a little more

general table you can look at it as the

general guidance

for the proof drug

the fundamental advantage is you can

modify the molecular property for

optimal bio performance

you can improve solubility permeability

and a target delivery

you could also gain the new chemical

entity with ip opportunity

but the challenge or the cons is

sometimes

and most time its very difficult to

predict or to manipulate in vivo

cleavage kinetics and this is very

important

and because its a treated new chemical

entity

and you have to submit a completely

different

tax package to fdas so to really take a

more time resource to develop such a

package

for nanoparticles

its a very

simple process its suitable for

dissolutionary limit absorption

and you can manufacture it with a good

physical stability

the challenge or cons is its not really

good for

drug with a high dose number

and really high drug loading of

nanoparticles could really have a

problem with the physical

with the physical stability

with lipidbased as i talked about you

have a lot of

advantages such as you dont have a

dissolution rate control process

you can really survive the drug

and

promote for better absorption

you can sustaining a supersaturated

state by ways to use the polynomial

and with lipid manufacturing processes

are most are just the mixing and feeling

in the capsule so much simple

and also one topic i didnt talk about

that the lipid can really try to direct

the drug absorption through lymphatic

process which is

a very

important but not really commonly needed

a pathway

the cons is

the solubility

of the drug may be very limited in the

vehicle means the functional acceptance

because its in the liquid state you may

not have the best chemical physical

stability we know the chemical stability

of the molecule in the liquid state are

much worse

than in a solid state

and you dont have many choice of the

solvent or surfactant used for

approved drug products so that means you

have very limited vehicle component to

be select

and some toxicity for chronic dose of

the excipients

for chronic dosing which might be

questionable

in contrast

the muffler solid

dispersion technology are most broadly

used now for for poorly water soluble

drugs

because you can really

improve the dissolution rate can try to

sustaining a supersatistate

you could have a diversified

manufacturer process which is you can

really choose the best for your drug

products

and also

the scientific understanding are much

be better now days

the cons is

the drug loading may be

limited and if you really have the

thermal sensitive drugs someone you may

not choose the hard extrusion which is

good causing the problem

the polymer

can be used for this technology

is limited too

but certainly with the four polynomial i

just just mentioned are most commonly

used

they can really trying to at least a

time being can satisfy our needs

one challenge is here you may have

looking into predictive along term

physical stability because the amount of

draw tend to be

have long term physical stability issues

you also have to have the looking the

packaging selection in order to make

sure the drug products are physically

stable

finally id like to give you more

my conclusions is

the biopharmaceutical property of the

new chemical entities are really dictate

the application of enabling formulation

technologies

for improving their bio availability

fundamentally if you have optimal new

chemical entities property

that would minimize the use of enabling

technology which is good

you normally you dont want to go to

actual miles to with enabling technology

which is really

will

have

resource and time

a requirement

however if you do cannot have

optimal

drug bio

pharmaceutical property we have to

choose the right technology based on

understanding of the drug molecules

such as also consider the drug loading

consider manufacturability and physical

stability so force in order to choose

the right

technology

finally

the scientific understanding

of the technology and understanding of

each

key attributes

of

such technology with relevance to the

drug are critical

lets really dictate the success of

failure

of the drug products

i selected list

the reference for major topics

listed here for your further

understanding

of

each enabling technology

this is certainly i just provide a very

short but ive maybe a little bias

but i find that if you really want to

learn each technology this might be an

easy way to identify this review

articles or research papers

try to get some ideas how this

technology can be

utilized

finally id like to

thank you very much for listening

um

if you have any questions please

submit the questions to the pcp course

a coordinator

id be happy to

further providing any uh

scientific

answers or trying to help you to

digest on this topic

certainly

further study on yourself probably will

be needed because this is a very complex

field today im just limited a very few

examples try to give you a fundamental

or quick overview of the technology

available

which is certainly not

in the right depths

id like to stop here and thank you

again