Lesson_7

Preformulation II

Dissolution, Permeability and BCS

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Learning outcomes

After learning this module you will be able to understand

- The concept of dissolution and theories
- Factors affecting dissolution
- Permeability study
- Basis of Biopharmaceutical Classification System (BCS) and its importance

Lesson Plan

- Dissolution: Goals, basic concept and theories
- Dissolution apparatus
- Factors affecting dissolution
- Permeability; Concept
- Determining Permeability: Diffusion Cellls
- BCS: Concept
- Class of drugs and examples
- Application of BCS

Dissolution

"Dissolution is defined as the process by which a known amount of drug substance goes into solution per unit of time under standardized conditions." It is used for characterizing the bio-pharmaceutical quality of a product at different stages in its lifecycle. It is used for choosing between different alternative formulations for further development. *Dissolution testing is an official test recommended by all pharmacopoeias (viz. official books) for evaluating drug release of solid and semisolid dosage forms.*

Dissolution: Goals

Dissolution aims for the prediction of *in vivo* performance, actually we can have some ideas how the drug is going to behave in the actual biological system, we can use it for assessing the lot-to-lot quality of a drug product or batch to batch consistency. For example; we have to produce a lot of 50000 tablets and then second lot is also there of 50000 tablets, how will you come to know that the both the batches are similar in performance with the help of dissolution we can predict that they are same in quality. Dissolution is a quality control test basically, it is used to guide development of the new formulation, to ascertain the need for *in vivo* comparative bioavailability and bioequivalence studies, it is mandatory requirement for regulatory approval, it is used to assess quality (stability/expiration dates) and optimization of the products.

Dissolution

Dissolution is drug going into the solution (media of GIT).

Dissolution: Concept

It is a two steps process

Step 1- Molecules are released from dosage form to media creating a saturated layer/stagnant layer, adjacent to the solid surface.

Step 2- Drug is diffused as per concentration gradient from higher concentration to lower concentration.

And it can be expressed with the help of Modified Noyes-Whitney's equation

$$\frac{dx}{dt} = \frac{A.D.K}{h} Cs - \frac{xd}{V}$$

- dx/dt is the dissolution rate,
- A is the surface area of the particle available for dissolution,
- D is the diffusion rate constant,
- K is the oil water partition coefficient,
- h is the thickness of the stagnant layer surrounding the particle,
- Cs is the saturation solubility of the drug,
- Xd is the amount dissolved of drug at time t and
- V is the volume of the dissolution media.

As far as the others parameters are concerned the surface area of drug, it is governed by particle size or the wettability. Surface area we are talking about the active surface area which is actually involved in that process of diffusion or dissolution. As far as the physiological conditions/properties are concerned which are governing this factor are surfactants in gastric juice and bile.

As far as the diffusion coefficient of drug is concerned it is governed by the molecular size and the viscosity of the luminal content while the motility pattern flow rate governed the stagnant layer thickness that thickness is modulated as per the motility pattern. pH, buffer capacity, bile and food composition effect the saturation solubility, hydrophilicity,

crystal structure and solubilization effect the solubility. Permeability governs the amount of drug already dissolved (Xd) while the secretions and co-administered fluids effect the volume of solvent available (V).

Dissolution: Factors

Factor	Physicochemical properties	Physiological properties
Surface area of drug (A)	Particle size, Wettability	Surfactants in gastric juice and bile
Diffusion coefficient of the drug (D)	Molecular size	Viscosity of luminal contents
Stagnant layer thickness (h)		Motility patterns and flow rate
Solubility (Cs)	Hydrophilicity, crystal structure, solubilization	pH, buffer capacity, bile and food composition
Amount of drug already dissolved (Xd)		Permeability
Volume of solvent available (V)		Secretion, co-administered Fluids

Dissolution: Theories

Dissolution can be explained with the help of some theories/ models. There are three major theories;

- Diffusion layer Model (Film Theory)
- Penetration or Surface Renewal Theory (Danckwerts' Model)
- Interfacial Barrier Model (Double Barrier Mechanism or Limited Solvation Theory)

Diffusion layer theory

It has two step process

- I - formation of a saturated stagnant layer around the drug particle in solution (Rapid step)
- II- Drug is slowly diffused from high to low concentration (Slow/ rate limiting step)

In the diffusion model, the diffusion is the rate limiting step.

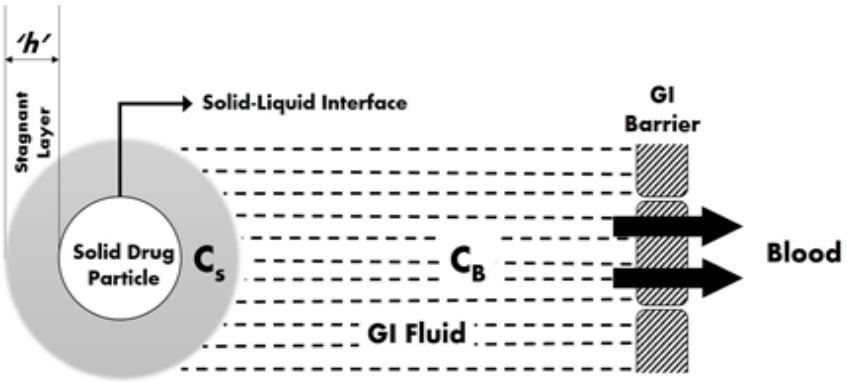


Fig. 1. Diffusion Layer Model

(Adapted from Semalty et al. Essentials of Pharmaceutical Technology, II edn, 2018, Pharma med Press, Hyderabad)

Surface renewal model

In this drug particle is continually exposed to fresh dissolution medium, numerous eddies or packets are there in the agitating medium. The solute diffuses in to the packets and is carried to the bulk medium. Unlike previous theory, no stagnant film layer is there due to turbulance/ constant surface renewal and that's why it is called surface renewal model.

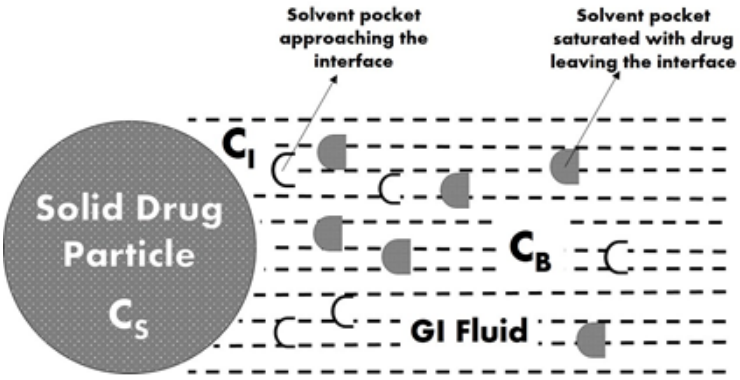


Fig. 2. Surface Renewal Model

(Adapted from Semalty et al. Essentials of Pharmaceutical Technology, II edn, 2018, Pharma med Press, Hyderabad)

Interfacial Barrier Model

In this model, it is also called limited solvation theory. A crystal undergoes dissolution through an interfacial process in the dissolving medium. The true surface area of the crystal must be considered. Each surface provides a different contribution to the dissolution process.

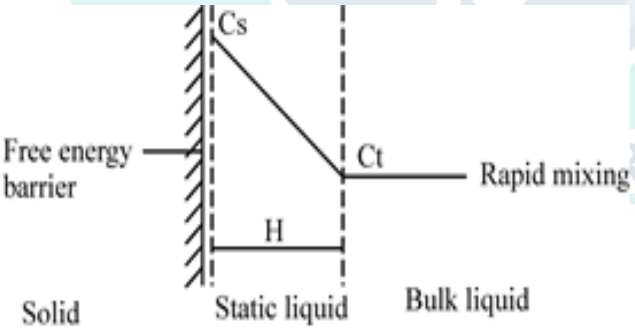


Fig. 3. Interfacial Barrier Model

(Adapted from Semalty et al. Essentials of Pharmaceutical Technology, II edn, 2018, Pharma med Press, Hyderabad)

And by this way the dissolution can be understood with the help of these three theories. And you can also learn the equation which express these

theories or models. So what we got here that dissolution is a process which is used for various aspects of drug delivery can be explained with the help of three major theories which must be understood with respect to the drug development.

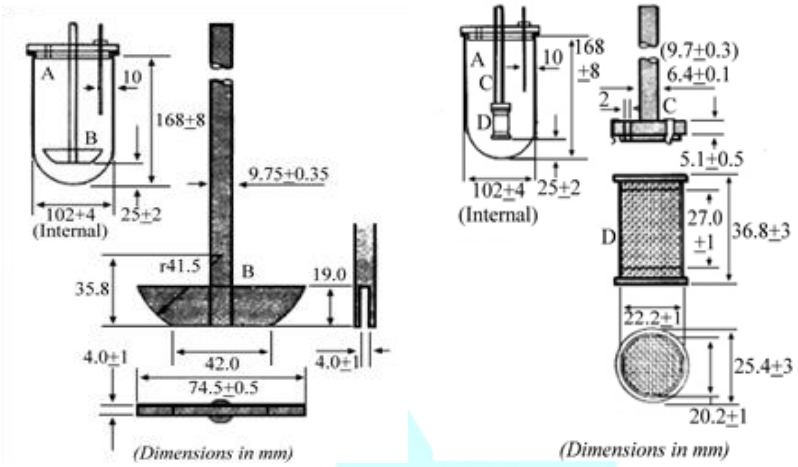
Dissolution Apparatus

These apparatus are designed in such a way that we try to mimicking/simulate the environment of gastrointestinal tract or the physiological conditions. It contains a jar, jar is of hemispherical bottom (bottom is hemispherical because intestine is hemispherical nature) to mimic that physiology. Volume we maintain to 900-1000 mL (viz. volume in the gastric environment) and that is simulated in this apparatus with keep that media in the range of 900-1000 mL. Temperature we maintain at just like as the body temperature around 37±1°C with the help of heaters in that apparatus. We provide the agitation with the help of motor guided paddle or basket to mimic the gastric motility. What is gastric motility? With the help of gastric motility the food content and the oral content move to the lower intestine and ultimately to the cecum or rectum. To mimic that motility, we give that agitation and that is helpful for the drug dissolution or permeation. And these apparatus may be single station or multi station (6, 8 or more assemblies are put together in dissolution apparatus)

Official Dissolution Test App. IP

These dissolution apparatus are standard, standard means each and every specification is final say for example in IP there are two types of official dissolution test apparatus (1) Paddle type apparatus is called type I apparatus and basket type apparatus is called type II apparatus. In both apparatus each and every specification is unique, you have to learn. Dear learners do remember each and every specification of length and diameter of each and every parts of dissolution test apparatus. It is important with respect to your viva-voce preparation. It is important with respect to your

GPAT examination. Please do learn and try to draw this diagram at least 10 times practice with each and every specifications



Paddle type (Type I) **Basket Type (Type II)**

Fig. 4 Dissolution Test Apparatus IP

Official Dissolution Test Apparatus USP

As far as the USP apparatus is concerned, USP prescribes seven dissolution test apparatus first two are the same but here type I is rotating basket remember this thing always. It is always asked, it is tricky question in some examination that in USP type I apparatus is rotating basket while IP type I apparatus is rotating paddle and in the type II USP apparatus it is rotating paddle and rest of the equipment are used only when these two first basket or paddle fails to perform this thing with respect to the requirement of the oral immediate release or modified release products, we can use these seven types of dissolution test apparatus, and you ca go through the further links for getting more information about each and every dissolution test apparatus prescribed by the USP.

Table 1. **Dissolution Test Apparatus USP**

App. No.	Description	General Application
1	**Rotating Basket**	**Oral IR and MR**
2	**Rotating Paddle**	**Oral IR and MR**
3	**Reciprocating Cylinder**	**Oral MR**
4	**Flow Through Cell**	**Oral MR**
5	**Paddle over disk**	**Transdermal DS**
6	**Cylinder**	**Transdermal DS**
7	**Reciprocating Holder**	**Transdermal DS or non-disintegrating oral MR**

***IR = Immediate release, MR = Modified Release, DS= Delivery System**

So we perform dissolution in dissolution test apparatus which are official and each and every thing is standard you know the size, shape, length, diameter of each and every part of the dissolution test apparatus is standard either in IP or USP. You must learn these things and this is helpful in having an idea about the drug release so dissolution test apparatus is very important with respect to study of drug release.

Now let me enter into the domain of the factors related to dissolution apparatus, we have discussed factors related to dissolution. Now we are discussing the factors of dissolution apparatus

Dissolution Apparatus factors

- **Type of apparatus**
- **Dissolution Medium**
- **Agitation**
- **Temperature**

Type of apparatus

We have discussed there are so many types of apparatus depending upon choice we can have things, we can select the apparatus.

Dissolution Medium

As far as the medium is concerned, as we have discussed that we try to mimic or simulate the environment, simulate the physiological conditions with respect to the Volume and pH or may be the presence or absence of some enzymes. We need try to have SIF (Simulated Intestinal Fluid) we will keep the pH 6.8, SGF (Simulated Gastric Fluid) we keep the pH 1.2, we use the phosphate buffer pH 6.8 and pH 1.2 acidic buffer in case of in case of SGF. We may add cosolvent or surfactant depending upon the requirement, it is not mandatory that we always try to mimic the nature of media sometimes we have entirely different type of media just to have a similar kind of dissolution profile as that of the standard drug when you are performing the bioequivalence studies. You will study it when you will be studying somewhere what is the bioequivalence, how is the bioequivalence is performed. We try to have that similar dissolution profile for that we select a suitable kind of media it may be completely different from the natural media presence in biological system.

FIP Recommended Dissolution Media

FIP recommends four major media

- 0.1N hydrochloric acid
- Buffer solution pH 4.5

- SIF without pancreatin pH 7.5
- 0.05M phosphate buffer solution of pH 5.8 to 8.0

Dissolution: rapid dissolving?

> An IR drug product is characterized as a rapid dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes using USP Apparatus I at 100 rpm or USP Apparatus II at 50 rpm in a volume of 900 mL or less of each of the recommended media**.**

(FIP recommends 4 dissolution media)

Agitation

We want to mimic gastric motility, our gastrointestinal tract motility starts from the GIT like this movement this kind of motility is there, to mimic this motility mild agitation conditions should be maintained during dissolution testing to allow maximum discriminating power. Agitation is done to detect products with poor in vivo performance, generally we keep the agitation 50-75- 100 rpm and in general it is mentioned in each and every monograph in your pharmacopoeias that what would be there agitation speed for particular kind of dissolution test apparatus and we can refer the official books pharmacopoeias for that agitation.

Temperature

Obviously it should be at the body temperature (37 ± 1 °C). Temperature of apparatus must be maintained before the beginning of test, you cannot do like that when you are starting it putting your tablet into the dissolution test apparatus and then you are starting you dissolution test apparatus. No it is not like that, when you prepare the cake in your microwave you preheat it you have to maintain the temperature before beginning the

process. So before starting the test you have to maintain the temperature at 37 $^{\circ}$C first and attained the temperature than the apparatus will maintain that. So what is the problem if we may not maintain the temperature, increase or decrease in temperature may effect the solubility, it may increase or decrease the solubility as well as the dissolution. So overall dissolution test may get affected if there is increase or decrease in temperature.

So what we got, that dissolution test apparatus are affected by the design, type of apparatus is there, kind of media you are using , kind of agitation or temperature you are providing whether you are maintaining the temperature or not. These are the major factors which are associated with the dissolution test apparatus.

Now let me enter into the domain of the permeability.

Permeability

Drug slowly dissolves goes into the solution and there after it passes across the biological membrane this is called permeability. Then and only then it gets absorbed, if a drug is found potent and active but if it is not permeated it wouldn't be absorbed, so permeability is very vital, it is very critical you cannot tolerate without permeability no absorption.

Permeability

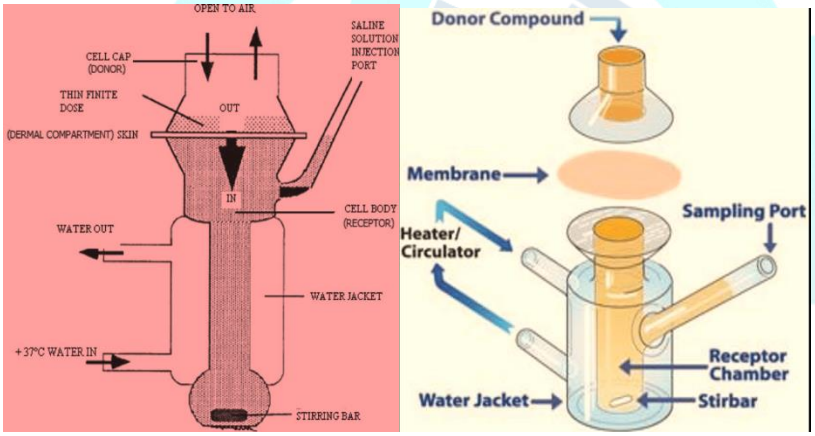
Permeability can be predicted by partition coefficient which we have explained in our one of the modules which we discussed in the first week that with the help of partition coefficient we can predict the permeability it depends on chemical nature, molecular weight and micro-environment of the drug. A drug substance is considered *highly permeable* (when the extent of intestinal absorption is determined to be 85% or higher it is called highly permeable). Permeability is assessed by the in vitro diffusion cells or in vitro permeation apparatus.

In vitro diffusion cells

Dear leaners let me give you the live demonstration of the in vitro diffusion cell. This is the invitro diffusion cell, this is very small instrument which is made up of glass as you can see it contains two compartments one is receptor compartment which is bigger as compared to the donor compartment. Donor compartment is placed on the receptor compartment and it is clamped with the help of these two clamps, see these are the clamp holders, with the help of them we can put them tightly closed what happens that in between these two compartments we can place a semi permeable membrane which may be natural intestine, natural skin or the artificial membrane which may be made of cellophane as you can see inside this receptor compartment is a internal compartment which is actually the receptor compartment which filled with pH 7.4 phosphate buffer as the receptor media. Generally the volume may be 3.5, 5 or may be 12.5 depending upon the requirement. And you can see the outer jacket it is there to water inlet, water outlet for maintaining the temperature of this whole assembly at the body temperature. What we do. We put the drug into the donor compartment, pre-wet drug is loaded here and we put this donor compartment on the receptor compartment in between that membrane is mounted and then the prefilled receptor compartment which is always on touch with this cellophane membrane what happens that drug starts diffusing from donor compartment slowly to the receptor compartment and for mimicking the agitation, we put small bead inside this receptor compartment and put it upon the magnetic stirrer, the agitation is given there with the help of magnetic stirrer that bead moves inside the receptor compartment and give the required agitation and with the passage of time this is the sampling port, we take out the sample 1mL or 0.5 mL or lesser amount and replace the same amount of pre-warmed media into this receptor compartment and by this way by analyzing the samples we can have the idea that with respect to time how much amount of drug is permeated across this membrane. So this is the purpose of in vitro diffusion cell.

So dear learners you have seen that this is a very small apparatus made up of glass and remember it is unofficial, it is not official in any pharmacopoeia design and fabrication differs from one model to another model depending upon the requirement or by the inventions made by some scientist like say for example there are two cells Franz diffusion cell and Keshary-Chein cell, you can see and learn the design of the these cells. These are called vertical diffusion cells. There are horizontal cells also please search the name of the horizontal diffusion cells.

So we have learnt that diffusion cells are required for the permeation studies. Give how the drug is permeating across the biological membrane, that permeation indication is given by the in vitro diffusion cell as the dissolution give the drug release profile. In the same way in vitro diffusion cell, gives the permeation profile.



(a) Franz Diffusion cell (b) Keshary-Chein (KC) cell

Fig. 5. Vertical Diffusion Cells

Biopharmaceutical Classification System (BCS)

BCS is Biopharmaceutical Classification System (BCS) it is a drug development tool Proposed by Amidon et al. in 1995 based on aqueous solubility and intestinal permeability the drugs are classified into four major classes.

The rate and extent of drug absorption from solid oral dosage forms depend on three things

- dissolution,
- solubility and
- Intestinal permeability

Biopharmaceutical Classification System (BCS)

Depending upon solubility and permeability Amidon 4 box model, it is classified into four classes;

Table 2. Biopharmaceutical Classification System (BCS)

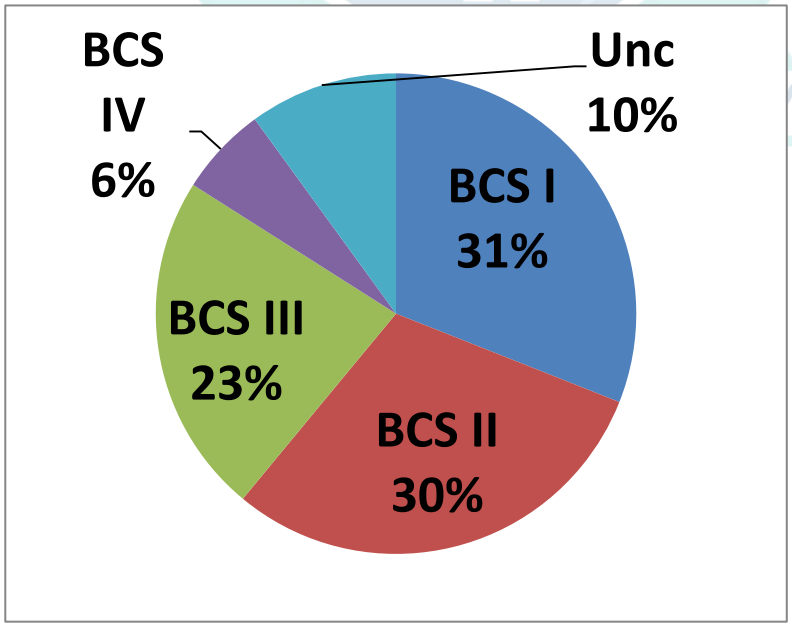
Class	Solubility	Permeability
I	**High**	**High**
II	**Low**	**High**
III	**High**	**Low**
IV	**Low**	**Low**

4 Box Amidon Model

1 **High Solubility** **High Permeability**	**2** **Low Solubility** **High Permeability**
3 **High Solubility** **Low Permeability**	**4** **Low Solubility** **Low Permeability**

Greater Prevalence of LS

In US if you go through the top 200 marketed drugs, BCS class I and class II are predominant, and if you see further new chemical entities the prevalence of low solubility drugs is as much as 70%. BCS class II drugs are 70%, so this is why the importance of BCS classification is there. That we can have some idea that we can develop the drugs which are having good biopharmaceutical properties with respect to solubility and the permeability.



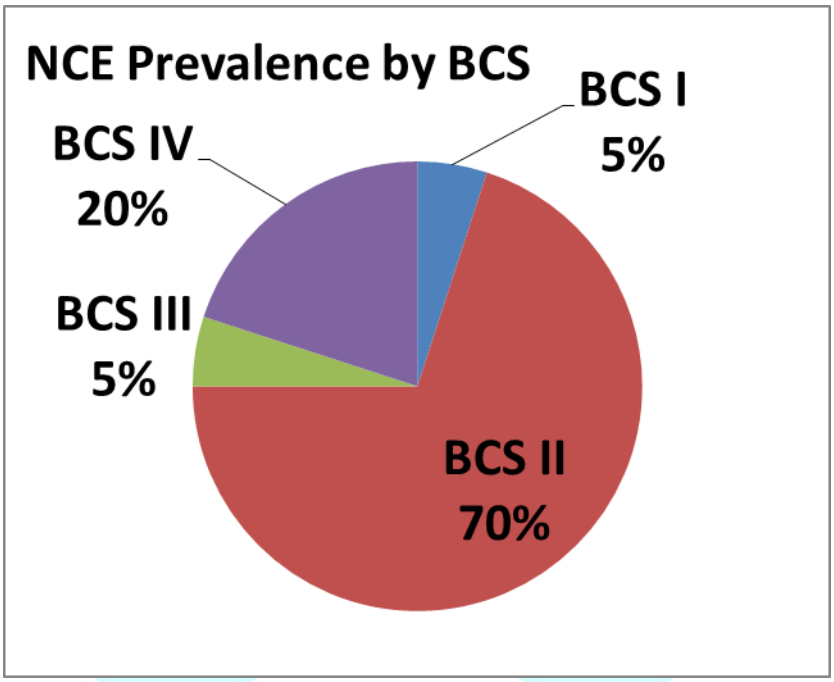


Fig. 6. Top 200 marketed drug USA by BCS;

(Source: Takagi et al 2006, Mol. Pharm., 2006; 3(6):631-43)

Solubility

As far as the solubility is concerned, in the BCS solubility is based on the highest dose strength in an Immediate Release product.

> "A drug substance is considered *highly soluble* when the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1.0-6.8."

> Remember it was the limit of pH 1-7.5 earlier, it has been reduced to pH 6.8 in the recent guidelines

Permeability

> Based directly on the extent of intestinal absorption in vivo in human or indirectly on the in vivo drug transfer across the human intestinal membrane as we performed in the diffusion cell .

"**A drug substance is considered *highly permeable* when the extent of intestinal absorption is determined to be 85% or higher."**

BCS

All the drugs can be classified into these four classes. Say for examples;

Class	Examples of the class
I	Rofecoxib, Paracetamol, Propranolol, Metoprolol,
II	Nimesulide, Nifedipine, Phenytoin, Digoxin
III	Acyclovir, atenolol, ranitidine, diphenhydr-amine
IV	Cyclosporin A, Furesamide

You can learn more of the examples of each of the class. Come back to us in discussion forum we can discuss the things also in the forum.

Now how to apply this thing how to apply BCS

BCS: Application

- For correlating the *in vitro* dissolution profiles with *in vivo* bioavailability of drugs
- For developing the *in vitro* dissolution specification
- For developing a strategy for improving the bioavailability of new chemical entities
- For predicting drug bioavailability: solubility or permeability limited.

This is the beauty of BCS that each and every aspect of drug development is need to know about the BCS class of particular drug

Take Away Message

- Dissolution, a QC test helps to predict the drug release, batch to batch consistency, in vivo performance, bioequivalence and is a regulatory requirement.
- Solubility, Dissolution and permeability govern the absorption of drug after oral ingestion.
- BCS is a drug development tool based on aqueous solubility and intestinal permeability of drugs.
- BCS classifies drugs in four classes (4 Box model).

Further Readings

- IP/USP
- Abdou HM, Theory of dissolution and Theoretical concepts for the release of a drug from a dosage form. In *Dissolution, Bioavailability and Bioequivalence,* Gennaro A., Migdalof B., Hassert G. L., Medwick T., Eds.; Mack Publishing Company: Easton, PA, 1989
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Credits/ References

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