Factors Affecting IVIVC

**Factors Affecting Development of a predictable IVIVC**

1. Physicochemical Properties of Drug
2. Composition of formulation
3. Method of manufacture
4. Complexity of the delivery system
5. Environmental factors during Dissolution

1. **Physicochemical properties of drug**

   A. **Factors affecting solubility**
   1. Polymorphism
   2. Amorphous state and solvation
   3. Free acid, free base or salt form
   4. Complexation, solid solutions and eutectics
   5. Particle size
   6. Surfactants

   B. **Factors affecting surface area available for dissolution**
   1. Particle size
   2. Manufacturing variables

   - The physicochemical properties of the drug substance can assume a primary role in controlling its dissolution from the dosage form.
   - The aqueous solubility of the drug is one of the major factors that determine its dissolution rate.
   - Some studies concluded that the drug solubility data can be used as rough predictor of the possibility of any future problems with bioavailability.
   - Some of the more prominent physicochemical properties of the drug that influence the dissolution rate are discussed below.

**Solid phase characteristics**

- Solid phase characteristics of drug, such as amorphicity, crystallinity, state of hydration and polymorphic structures have significant influence on dissolution rate.
- Anhydrous forms dissolve faster than hydrated form because they are thermodynamically more active than hydrates. Eg. Ampicillin anhydrate has faster dissolution rate than trihydrate.
- Amorphous forms of drug tend to dissolve faster than crystalline materials.
- E.g. Novobiocin, Griseofulvin, Phenobarbital, cortisone acetate and chloramphenicol.
- However, dissolution rate of amorphous erythromycin estolate is markedly lower than the crystalline form of erythromycin estolate.
Polymorphism
- Polymorphic forms of a drug substance are indicative of different crystalline forms. With a change in the crystalline form, there is a change in the lattice energy level associated with each form.
- This energy is responsible for physicochemical properties such as solubilizing potential and dissolution rate.
- Metastable (high activation energy) polymorphic forms have better dissolution than stable forms.
- This phenomenon is particularly applicable to steroids.
- As a result, crystallographic modifications can significantly influence dissolution of drug substance itself as well as the dosage unit it is contained within.

Coprecipitation and/or complexation
- In most cases, coprecipitation and complexation is employed for enhancing the dissolution of the drug substance. The mechanism for the enhanced dissolution may be the formation of the energetic amorphous drug state.
- Eg. Hydroflumethiazide- PVP complex

Salt formation
- It is one of the common approaches used to increase drug solubility and dissolution rate. It has always been assumed that sodium salts dissolve faster than their corresponding insoluble acids. Eg. sodium and potassium salts of Penicillin G, sulfa drugs, phenytoin, barbiturates etc.
- Same is the case for weak base drug, strong acid salts, such as hydrochlorides and sulphates of weak bases such as epinephrine, tetracycline are commonly used due to high solubility.
- However, free bases of chlortetracycline, methacycline were more soluble than corresponding hydrochloride salt at gastric pH values, due to common ion suppression.

Particle size
- There is a direct relationship between surface area of drug and its dissolution rate. Since, surface area increases with decrease in particle size, higher dissolution rates may be achieved through reduction of particle size.
- Micronization of sparingly soluble drug to reduce particle size is by no means a guarantee of better dissolution and bioavailability.
Micronization of hydrophobic powders can lead to aggregation and floatation when powder is dispersed into dissolution medium. So, mere increase in S.A. of drug does not always guarantee an equivalent increase in dissolution rate. Rather, it is increase in the “effective” S.A., or area exposed to dissolution medium and not the absolute S.A. that is directly proportional to dissolution rate.

Hydrophobic drugs like phenacetin, aspirin shows decrease in dissolution rate as they tend to adsorb air at the surface and inhibit their wettability. Problem eliminated by evacuating surface from adsorbed air or by use of surfactants. So these drugs in-vivo exhibit excellent wetting due to presence of natural surfactants such as bile salts.

Factors related to the composition and method of manufacture

A. Tablets
   a. Amount and type of the diluent or filler and other adjuvants
   b. Type of tablet manufacture employed
   c. Granule size and size distribution
   d. Amount and type of disintegrant and method of incorporating it
   e. Amount and type of surfactant (if any) and method of incorporating it
   f. Compressional force and speed of compression

B. Capsules
   a. Amount and type of diluent or filler and other adjuvants
   b. Method used to reduce bulk (granulating or slugging)
   c. Granule or powder size and size distribution
   d. Amount and type of lubricant and method of incorporating it
   e. Amount and type of surfactant (if any) and method of incorporating it
   f. “Pressure” applied during filling
   g. Composition and properties of capsule shell

2. Factors related to Composition of formulation

Most solid dosage forms incorporate more than one excipient for various purposes together with the active ingredient in the formulation. The dissolution rate of a pure drug can be altered significantly when mixed with various adjuncts.

These adjuncts include diluents, binders, lubricants, granulating agents, disintegrants, etc.

Excipients and additives

Studies of starch on dissolution rate of salicylic acid tablet by dry double compression process shows three times increase in dissolution rate when the starch content increases from the 5 – 20 %.

Here starch particles form a layer on the outer surface of hydrophobic drug particles resulting in imparting hydrophilic character to granules & thus increase in effective surface area & rate of dissolution.
Different types of dissolution apparatus utilized affect ranking of different varieties of starch. With stirring type of agitation, order was potato starch > cornstarch > arrowroot starch > rice starch. With oscillating type, a different order observed. Corn > rice > arrowroot > potato.

The dissolution rate is not only affected by nature of the diluent but also affected by excipient dilution (drug/excipient ratio).

E.g. in quinazoline comp. dissolution rate increases as the excipient /drug ratio increases from 3:1 to 7:1 to 11:1.

**Binders and granulating agents**

- Phenobarbital tablet granulated with gelatin solution provide a faster dissolution rate in human gastric juice than those prepared using Na – carboxymethyl cellulose or polyethylene glycol 6000 as binder.
- Gelatin imparts hydrophilic character to hydrophobic drug surface whereas PEG 6000 forms a poorly soluble complex with poor solubility and NA-CMC is converted to its less soluble acid form at the low pH of gastric fluid.
- Even gelatin obtained from various processes and origins affect the dissolution rate of dosage forms. Using Phenobarbital as test drug the fastest dissolution rate was observed with 2 % gelatin, while decrease in dissolution rate was observed with 4% gelatin content. This was due to higher concentration which formed a thick film around tablet upon drying of the granules.

- The hydrophilic binder increases dissolution rate of poorly wettable drug.
- Large amt. of binder increase hardness & decrease disintegration/dissolution rate of tablet.
- A non aqueous binder such as ethyl cellulose retards the drug dissolution.

**Disintegrating agents**

- Type and amount of disintegrating agent employed in the formulation significantly controls the overall rate of dissolution of the dosage form.
- Disintegrating agent added before & after the granulation affects the dissolution rate. Studies of various disintegrating agents on Phenobarbital tablet showed that when copagel (low viscosity grade of Na CMC) added before granulation decreased dissolution rate but if added after did not had any effect on dissolution rate and primojel (sodium glycolate of potato starch) was not found to be effective particularly on addition after granulation.
- Microcrystalline cellulose is a very good disintegrating agent but at high compression force, it may retard drug dissolution.
- Starch is not only an excellent diluent but also superior disintegrant due to its hydrophilicity and swelling property.
- Disintegration and dissolution rate of disintegrants with moderate swelling capacity depend to a large extent on mixing time of drug/excipient preblended with lubricant. On other hand, disintegrants with strong swelling capacity such as sodium starch glycolate were hardly affected by mixing time with lubricant.

**Lubricants**

- Lubricants that are commonly incorporated in the formulation of solid dosage forms fall predominantly in the class of hydrophobic compounds.
- The nature, quality, quantity and method of addition of the lubricant can affect the dissolution rate. It should be added in small amount (1% or less) and should be tumbled or mixed gently for only very short time. Prolonged mixing increases the dissolution time.
- Stearates and talc are hydrophobic in nature tend to retard the dissolution rate by decreasing the effective surface drug – solvent interfacial area by changing the surface characteristics of the tablets, which reduces wettability and prolonging its disintegration time.
- If an enhancing effect in dissolution of hydrophobic granules is desired, water soluble lubricant such as SLS or CARBOWAXES may be used.

**Surfactants**

- They enhance the dissolution rate of poorly soluble drug. This is due to lowering of interfacial tension between the drug and dissolution medium, increasing effective surface area, which in turn results in faster dissolution rate.
- Additionally, the method of incorporation of surfactant in the drug product formulations can markedly affect the dissolution characteristics of the relatively hydrophobic drug.
- E.g Non-ionic surfactant Polysorbate 80 increase dissolution rate of phenacetin granules. The increase was more pronounced when the surfactant was sprayed on granules than when it was dissolved in gelatin as granulating agent.

**Water soluble dyes**

- Dissolution rate of single crystal of sulphathiazole was found to decrease significantly in presence of FD&C Blue No.1. The inhibiting effect was related to preferential adsorption of dye molecules on primary dissolution sources of
crystal surfaces. They inhibit the micellar solubilization effect of bile salts on drug.
- Cationic dyes are more reactive in lower conc. than are anionic dyes.

Coating polymers
- Tablets with MC coating were found to exhibit lower dissoln profiles than those coated with HPMC at 37ºC. The differences are attributed to thermal gelation of MC at temp near 37º, which creates a barrier to dissoln process & essentially changes the dissoln medium. This mechanism is substantiated by the fact that at temp below the gel point & at increased agitation, the effect disappears.

3. Method of manufacture

Method of granulation
- Granulation process in general enhances dissolution rate of poorly soluble drug. Wet granulation is traditionally considered superior to a dry or double compression procedure. It improves dissolution rates of poorly soluble drugs by imparting hydrophilic properties to the surface of the granules. But exception is the dissolution profile of sodium salicylate tablets prepared by both wet granulation and direct compression where the dissolution was found more complete and rapid in latter case.
- A newer technology called as APOC “Agglomerative Phase of Comminution” was found to produce mechanically stronger tablets with higher dissolution rates than those made by wet granulation. A possible mechanism is increased internal surface area of granules produced by APOC method.

Granule size
- The nature of the granule affects the dissolution rate of the dosage form. The granule size has little effect on the dissolution rate if the granules are relatively soft and disintegrate easily. However, if they are harder and disintegrate more slowly, the granule size will be of importance and an increase in size will cause a decrease in dissolution rate.

Compression force
- The compression process influence density, porosity, hardness, disintegration time & dissolution of tablet.
  - First condition, higher compression force increase the density & hardness of tablet, decrease porosity & hence penetrability of solvent into the tablet retard the wettability by forming a firmer & more effective sealing layer by the lubricant and in many case tighter bonding between the particle so decrease dissolution rate of tablet.
  - Second condition, higher compression force cause deformation, crushing or fracture of drug particles into smaller ones or convert spherical granules into disc shaped particles with a large increase in the effective surface area so increase in dissolution rate.
Combination of both conditions can occur

In short dissolution decrease at lower pressure (better bonding), then increase at higher pressure (crushing effect) and decrease again with further increase in pressure bcz of extra rebonding and formation of denser tablets with poorer dissolution characteristics.

**Drug-excipient interaction**

- These interactions occur during any unit operation such as mixing, milling, blending, drying, and/or granulating result change in dissolution.
- The dissolution of prednisolone found to depend on the length of mixing time with Mg-stearate
- Similar as increase in mixing time of formulation containing 97 to 99% microcrystalline cellulose or another slightly swelling disintegrant result in enhance dissolution rate.
- Polysorbate-80 used as excipient in capsules causes formation of formaldehyde by autoxidation which causes film formation by denaturing the inner surface of capsule. This causes decrease in dissoln rate of capsules.

**Storage of dosage form**

- The effect of aging of tablets, capsules and other solid dosage forms should always result in a decrease in a dissolution rate. However, an increase in dissolution rate may also be found. In many cases, however, there is no effect at all.
- Dissolution rate of Hydrochlorothiazide tablets granulated with acacia exhibited decrease in dissolution rate during 1 yr of aging at R.T. A similar decrease was observed in tablets stored for 14 days at 50-80°C or for 4 weeks at 37°C.
- For tablets granulated with PVP there was no change at elevated temperature but slight decrease at R.T. Tablets with starch gave no change in dissoln rate either at R.T. or at elevated temperature.

**4. Factors related to complexity of delivery system**

- Among the most significant factors that control the process of dissolution are the type and nature of the dosage form within which the active ingredient is contained.
- The process of dissolution of an active ingredient from solid pharmaceutical dosage forms involves several intermediate physicochemical steps, such as wetting, swelling capillarity, solubility and diffusion.
- With the exception of non disintegrating dosage forms, most solid dosage forms undergo a somewhat common sequence of events during the process of dissolution in vitro.
- These events can be delineated as three different types of descriptive categories:
  1) Process parameters
## Theoretical parameters

### Wetting of dosage unit
- The first step in the process of dissolution is the wetting of the external surface of the dosage form. The degree and extent to which the surface is wetted are a function of the interfacial tension at the solid liquid interphase. Additionally, the process of wetting is a function of the contact angle the liquid makes with the solid surface.
- The more hydrophobic the powder is, the slower the wetting and subsequent penetration of the dissolution medium across the solid surface barrier.
- In the case of the tablets, granules prepared by the wet granulation process can produce lower contact angle values, a result attributed to the hydrophilization phenomenon associated with hydrophobic surfaces, thus promoting wetting.

### Deaggregation /deagglomeration
- Most conventional dosage forms undergo some form of deaggregation and /or deagglomeration prior to dissolution.
- The greater the degree of compaction, the smaller will be the average pore radius, which results in larger time for deaggregation.
- In case of tablet the pore size through which the dissolution medium must penetrate to effect deaggregation is much smaller than in a capsule.
- To overcome this difficulty, disintegrants are employed to assure more efficient penetration and complete deaggregation.
- The disintegrants swell and result in physical breaking apart of the intact tablet.

### Dissolution of powders
- The process of dissolution of powders is a function not only of the particulate dimensions (size, shape, effective surface area, etc.), but also of the micromeretic properties, such as particle size distribution.
- Additionally, factors such as contact angle, wettability, and physicochemical properties of the drug particles have a significant bearing on the dissolution performance of the powder.

## Dissolution testing device parameters

<table>
<thead>
<tr>
<th>Process</th>
<th>Parameters modelistic (theoretical)</th>
<th>Dissolution testing Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction of dosage form in dissolution medium</td>
<td>Wetting of dosage form</td>
<td>Type of device</td>
</tr>
<tr>
<td>Sampling</td>
<td>Penetration of dissolution medium into the dosage unit</td>
<td>Operating characteristics</td>
</tr>
<tr>
<td>Assay</td>
<td>Deaggregation and /or deagglomeration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wetting of drug</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solubilization /dissolution of the drug</td>
<td></td>
</tr>
</tbody>
</table>
Dissolution of capsules

- Capsules must have the capsule shell dissolved before the contents are available to the gut fluids for dissolution irrespective of it being a hard or a soft gelatin capsule.
- Both the manufacturing process itself and the inert ingredients in the final product can affect the dissolution rate of the drug from the dosage form.
- Other factors that may influence bioavailability from capsule dosage forms include particle size, selection of diluents and fillers, adsorption, and other interactions of drug and fillers and crystal form of drug.

![Dissolution of Capsule Shell Diagram](image)

- Major problems associated with the dissolution testing of capsules that can significantly alter the dissolution process are:
  - Floating of the dosage form during the dissolution test, this is circumvented by localizing the dosage unit at convenient position of the dissolution medium. This is achieved by either restraining the capsule in a stainless steel gauge or by allowing the capsule to move in a restricted volume.
  - The dissolving gelatin shell sometimes tends to clog the pores of the basket or form barrier film along the outer surface of the restrainer.
  - This results in an apparent increase in lag time before the shell gets ruptured and contents are made available for absorption.
  - In many instances poor IVIVC as well as uncomparable rank order correlations can be attributed to the prevalence of a sum total of the multitude of such effects during the dissolution process of capsules.

Dissolution of tablets

- There are primarily two pathways via which the drug entity is made available to the dissolution medium. Either the tablet disintegrates thereby exposing the drug contents to the medium or the dissolution process continues without the disintegration of the tablet.
The rate of dissolution of a drug substance in solid form from a granule or a tablet depends to a large extent on its solubility in the solvent phase and its concentration in that phase.

Surface area of the solid dosage form will change during the dissolution process. The change in surface area alters the fluid flow dynamics involved in the dissolution rate constant. Such an effect is more pronounced in disintegrating dosage forms than in nondisintegrating types. Nondisintegrating dosage forms gradually reduce their surface area during the dissolution process.

Disintegrating forms are subject to complicated disintegration and deaggregation as they release particles of various sizes and specific gravities into the solvent stream. Any one of the processes—disintegration, deaggregation and dissolution—may vary in time. In some cases one or the other may be rate limiting.

Additionally, the rate of shear of fresh dissolution medium in contact with the surface area of the solid varies with particle size, shape and density.

**Dissolution of suppositories**

One basic problem in testing for drug release from suppository is the change in the physical dimensions of the suppository (due to softening, deformation, melting or disintegration) during the test results in exposing a variable interfacial area to the dissolution medium. The variability of this factor leads to poor test reproducibility since the release rate depends on the interfacial area.

The need to control interfacial area is important, the introduction of an additional physical process (membrane transport) complicates matters and may mask the true release characteristics for certain drug suppository base combinations.

**Dissolution of suspensions**

Since tablets and capsules disintegrate into powder suspensions, pharmaceutical suspensions share the dissolution process as a rate limiting for absorption and bioavailability.

The dissolution rate is dependent on the solute diffusion coefficient, solubility and density of the suspended solid. The solubility of the drug (suspended material) may be manipulated by additives such as by addition of a surfactant or complexing agent.

Slim to poor IVIVC have been common to those formulations. This can be attributed to the lack of simple method to obtain narrow populations of
suspended material of varying sizes (in the micrometer range), which poses a problem in establishing the optimum size requirement of a suspension product.

**Dissolution of modified release dosage forms**

- All factors that affect the dissolution performance of any conventional dosage form affect the dissolution of modified release dosage forms. Additionally, prolonged residence time in the biological space can contribute to the dissolution behavior of such dosage forms. Hence they are exposed to a milieu of varying pH in the gut (pH approaching 1.2 in the acid secreting stomach region to pH approaching 7.8 in the distal region of the intestinal tract).
- They are especially important since most of the modified release dosage forms incorporate modifications in the structural components of the dosage unit such as crystallographic changes of the drug molecule, modifications in the dissolution surface, etc. as well as diffusion rate modifications.
- If modified release is obtained by using enzymatic breakdown and if the enzymatic hydrolysis follows first order kinetics, the drug release process also follows the first order kinetics.
- Several other factors of equal importance— including particle size, crystal surface anisotropy, the drug’s solubility, diffusion layer thickness, partition and diffusion coefficients, viscosity, molecule size, and concentration gradient difference— have a bearing on the dissolution performance of modified release products.
- The reproduction of gut conditions in vitro has always been a problem despite the construction of the apparatus.

5. **Environmental factors during Dissolution**

**A. Factors related to the dissolution testing apparatus**

1) **Eccentricity of agitating (stirring) element**
   - Official compendium specifies that the stirring shaft must rotate without significant wobble. Eccentricity can induce and propagate changes in hydrodynamic conditions and flow patterns that can influence the dissolution behavior of the product.

2) **Vibration**
   - It can affect change in the flow patterns of the dissolution medium. Additionally, it can introduce unwanted energy to the dynamic system. Both effects may result in significant changes in dissolution rate.
   - It must be noted that no device is free of vibration. The objective of conducting dissolution testing should be to reduce vibration from external sources to a manageable level that will not introduce significant variation in results from successive dissolution tests on the same product.

3) **Agitation intensity**
   - Relationship between intensity of agitation and rate of dissolution varies considerably acc. to type of agitation used, the degree of laminar and turbulent flow in system, the shape and design of stirrer and physicochemical properties of solid.
Speed of agitation generates a flow that continuously changes the liq/solid interface between solvent and drug. In order to prevent turbulence and sustain a reproducible laminar flow, which is essential for obtaining reliable results, agitation should be maintained at a relatively low rate.

Thus, in general relatively low agitation should be applied.

BASKET METHOD - 100 rpm
PADDLE METHOD - 50-75 rpm

4) Stirring element alignment
USP states that the axis of the stirring element must not deviate more than 2 mm from the axis of the dissolution vessel.
A series of tests suggest that a tilt in excess of 1.5° may increase in dissolution rates using method 2 from 2 to 25%.

5) Flow pattern disturbances
For dissolution rate data to be reproducible and reliable, the flow pattern should be consistent from test to test

6) Sampling probes, position and filters
Sampling probe can affect the hydrodynamic of the system & so that change in dissolution rate.
For position of sampling, USP / NF states that sample should be removed at approximately half the distance from the basket or paddle to the surface of the dissolution medium and not closer than 1 cm to the side of the flask.
Filter material must be saturated with the drug by repeated passage to avoid losses that might go undetected during the test sampling.
Accumulation of the particulate matter on the filter surface may cause significant error in the dissolution testing.
The practice would be to purge the filter with a reversed flow of dissolution medium or air at the end of each sample interval.

7) Dosage form position
Change in the design of any dissolution testing device can alter the position of the dosage form in the dissolution medium. Additionally, with this changes there will bw significant changes in the fluid flow patterns induced the system. These can markedly influence the dissolution characteristics of the dosage form being tested.
The dissolution data show definite tablet position dependency effects. This is important in dissolution testing for tablets in general and for multilayered tablets in particular.

8) Type of device
Different dissolution testing devices offer different working conditions, depending on their mechanics. Also the drawbacks associated with each type of apparatus as well as systemic errors associated with some of the official methods of dissolution can significantly alter the dissolution rate determinations.
## Random input variables influencing dissolution testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Maximum allowable</th>
<th>Excess commonly seen</th>
<th>Methods of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Eccentricity</td>
<td>+/- 2 mm (compendium)</td>
<td>2 - 5 mm</td>
<td>Straighten shafts; use wide shaft guide points</td>
</tr>
<tr>
<td>2. vibration</td>
<td>0.1 mil displacement at vessel</td>
<td>.2 - .9 mil</td>
<td>Eliminate source</td>
</tr>
<tr>
<td>3. Alignment</td>
<td>1.5° to perpendicular</td>
<td>2 - 7°</td>
<td>Adjust alignment in field</td>
</tr>
<tr>
<td>4. Centering</td>
<td>+/- 2 mm (compendium)</td>
<td>+/- 2 - 6 mm</td>
<td>Center individual flasks</td>
</tr>
<tr>
<td>5. Agitation rate</td>
<td>+/- 4 %</td>
<td>+/- 10 %</td>
<td>Use better, smooth control, or synchronous device</td>
</tr>
<tr>
<td>6. Dissolved gas</td>
<td>Deaerated</td>
<td>Bubbles form</td>
<td>Deaerate media by various methods</td>
</tr>
<tr>
<td>7. Media pH</td>
<td>0.00 accuracy</td>
<td>+/- .05</td>
<td>Check buffers or deaerate; calibrate the pH meter</td>
</tr>
<tr>
<td>8. Media contamination</td>
<td>ppm</td>
<td>Ions, surfactants</td>
<td>Carefully control media</td>
</tr>
<tr>
<td>9. Evaporation</td>
<td>None</td>
<td>2 - 5 %</td>
<td>Use flask covers</td>
</tr>
<tr>
<td>10. Temperature</td>
<td>+/- 0.05 (compendium)</td>
<td>1 - 2°</td>
<td>Monitor individual flasks; allows adequate equilibrium</td>
</tr>
<tr>
<td>11. Flow pattern</td>
<td>No interference</td>
<td>Turbulence from probes</td>
<td>Remove probes</td>
</tr>
<tr>
<td>12. Sampling position</td>
<td>Compendium</td>
<td>+/- 0.5 cm</td>
<td>Use care</td>
</tr>
<tr>
<td>13. Filters</td>
<td>No sorbing</td>
<td>Considerable blockage</td>
<td>Use bidirectional filter flow; check sorbing</td>
</tr>
<tr>
<td>14. Detection</td>
<td>Use standard</td>
<td>Interference</td>
<td>Use standard</td>
</tr>
<tr>
<td>15. Sorbtion</td>
<td>None</td>
<td>Considerable</td>
<td>Check materials</td>
</tr>
</tbody>
</table>

### B. Factors related to dissolution test parameters

1) **Temperature**
   - Drug solubility is temperature dependent, therefore careful temperature control during dissolution process is extremely important.
   - Generally, a temp of 37° ± 0.5 is maintained during dissolution determination of oral dosage forms and suppositories. However, for topical preparations temp as low as 30° and 25° have been used.
2) **Dissolution medium**

It is very imp factor affecting dissolution and is itself affected by number of factors such as

**I. Dissolution composition media and pH**

- Dissolution rate of the drug products can be influenced by both the composition and pH of the dissolution medium. During the dissolution testing of the benzoic acid tablets when various concentrations of sodium chloride, sodium sulfate, and dextrose were added to the dissolution medium there is decrease in dissolution rate.
- For Weak acids, dissoln rate increases with increase in pH whereas for weak bases, increase with decrease in pH.

**II. Volume of dissolution medium and sink conditions**

- If drug is poorly soluble, a relatively large amount of fluid should be used if complete dissolution is to be expected.
- In order to minimize the effect of conc. gradient and maintain sink conditions, the conc. of drug should not exceed 10-15% of its max. solubility in dissoln medium selected. For most of the drugs about 1 L is more than sufficient to maintain sink conditions.
- However, some insoluble drug present a problem as to handling of huge vol of dissoln medium that would be required to maintain the sink conditions. For these, different approaches have been tried like
  - continuos flow method where fresh solvent is pumped continuously into dissoln flask at a fixed flow rate while maintaining a constant volume.
  - Use of non-ionic surfactant in conc. above CMC.
  - Use of alcoholic solution (10-30%).

**III. Dissolved gases – air**

- In the dissolution testing occurrence of air can interfere with reproducibility of the results in a number of ways.
- Dissolved air in distilled water could significantly lower its pH and consequently affect the dissolution rate of drugs that are sensitive to pH changes, weak acids. Another effect is to be released from the medium in form of tiny air bubbles. These bubbles collect at the surface of the dosage forms, thereby acting as a hydrophobic barrier between solvent and solid surface. This inhibits wetting and reduction of S.A. and lower dissoln rate.

**IV. Viscosity**

- Dissolution rate decreases with increased viscosity of the dissolution medium especially in the case of diffusion – controlled dissolution processes. Viscosity can have very little effect on inter facial controlled dissolution process.

**References:**

- Pharmaceutical dissolution testing, Umesh V. Banakar
- Dissolution, bioavailability & bioequivalence, Hamed M. Abdou.

**Questions:** Write short note on factors affecting IVIVC. (LM; uni. 04, 07)