▪ FACTORS AFFECTING DISSOLUTION RATE

Divided into five classes-

a. Physicochemical Properties of Drug
b. Drug Product Formulation Factors
c. Processing Factors
d. Factors Relating Dissolution Apparatus
e. Factors Relating Dissolution Test Parameters

I. PHYSICOCHEMICAL PROPERTIES OF DRUG-

1. DRUG SOLUBILITY-

- Solubility of drug plays a prime role in controlling its dissolution from dosage form. Aqueous solubility of drug is a major factor that determines its dissolution rate. Minimum aqueous solubility of 1% is required to avoid potential solubility limited absorption problems.
- Studies of 45 compound of different chemical classes and a wide range of solubilities revealed that initial dissolution rate of these substances is directly proportional to their respective solubilities.
- Fig shows a log-log plot of solubilities of several drug Vs their corresponding intrinsic rates of dissolution at infinite rotation speed. Evident from graph that compounds with high solubilities exhibit significantly higher dissolution rates.

2. 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 Peniciilin G, sulfa drugs, phenytoin, barbiturates etc.
- While in case of Phenobarbital dissolution of sodium salt was slower than that of weak acid. Same is the case for weak base drug, strong acid salts, such as hydrochlorides and sulphates of weak bases such as epinephrine, tetracycline

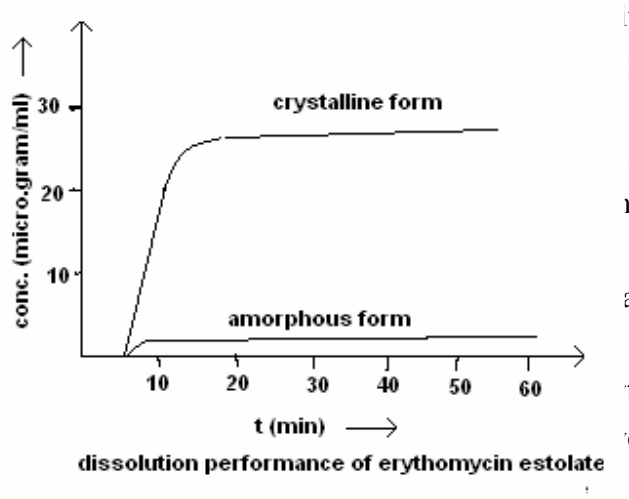
are commonly used due to high solubility. However, free bases of chlortetracycline, methacycline were more soluble than corresponding hydrochloride salt at gastric pH values, due to common ion suppression.

3. 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 dissoln 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.

4. SOLID STATE CHARACTERISTICS-

- Sol ty, crystallinity, state of hyc influence on dissolution rate
- An form bcz they are the picillin anhydrate faster dis
- An an crystalline materials. E.g
- Wh **thromycin estolate** is ma cin estolate.



dissolution performance of erythomycin estolate

- Metastable (high activation energy) polymorphic forms have better dissolution than stable forms.

5. **CO-PRECIPITATION-**
   - Dissolution rate of sulfathiazole could be significantly increased by co-precipitating the drug with povidone. .
6. **SHAPE OF THE TABLET**

   Affects dissolution of the tablet.

Note : in case of CONTROLLED RELEASE tablets high rpm should be applied to check for robustness and dose dumping.

II. DRUG PRODUCT FORMULATION FACTORS

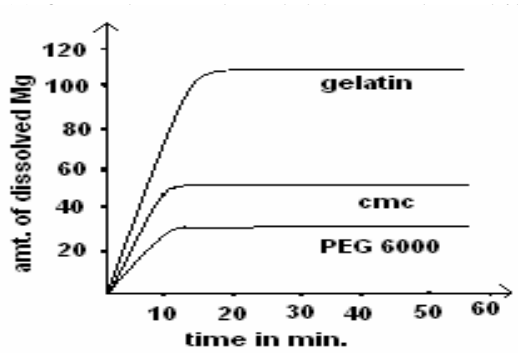
- Dissolution rate of pure drug can be altered significantly when mixed with various adjuncts during manufacturing process such as diluents, dyes, binders, granulating agents, disintegrants and lubricants.
- Generically identical tablet or capsules exhibited differences in their dissolution rates of their active ingredients.

1. **DILUENTS-**
   - Diluent in capsule & tablet influence the dissolution rate of drug.
   - 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 increase 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>arrowrootstarch>ricestarch. With oscillating type, a diiferent 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.

2. **DISINTEGRANTS-**
   - Disintegrating agent added before & after the granulation affect 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.
   - **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.

3. **BINDERS AND GRANULATING AGENTS-**
   - The hydrophilic binder increase dissolution rate of poorly wettable drug.
   - Large amt. of binder increase hardness & decrease disintegration /dissolution rate of tablet.
   - Non aqueous binders such as ethyl cellulose also retard the drug dissolution.
   - **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 imparted hydrophilic character to hydrophobic drug surface whereas PEG 60 CMC was converted to its less
   - In Phen rved with 10% gelatin wherea This was due to higher concent
   - Water aster dissolution rate compar



4. LUBRICANTS-

- Lubricants are hydrophobic in nature (metallic stearates) and prolong tablet disintegration time by forming water repellant coat around individual granules. This retarding effect is most imp factor in influencing rate of dissolution of solid dosage forms.
- Both amount and method of addition affect the property. It should be added in small amount (1% or less) and should be tumbled or mixed gently for only very short time. Prolonged mixing the dissolution time.
- However, if an enhancing effect in dissolution of hydrophobic granules is desired, water soluble lubricant such as **SLS** or **CARBOWAXES** may be used.

5. SURFACTANTS-

- They enhance the dissolution rate of poorly soluble drug. This is due to lowering of interfacial tension, increasing effective surface area, which in turn results in faster dissolution rate.
- 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 granulating agent.

6. 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.

7. 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.

III. PROCESSING FACTORS

1. METHOD OF GRANULATION-

- Granulation process in general enhances dissolution rate of poorly soluble drug. Wet granulation is traditionally considered superior. 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.

2. 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 condition 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.

3. UNIT OPERATIONS INVOLVED.

- 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.

4. STORAGE CONDITIONS-

- Dissolution rate of Hydrochlorthiazide tablets granulated with acacia exhibited decrease in dissolutionrate during 1 yr of aging at R.T. A similar decrease was observed in tablets stored for 14 days at 50-80ºC or for 4 weeks at 37ºC.
- 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.

IV. FACTORS RELATING DISSOLUTION APPARATUS

1. AGITATION-

- 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

2. STIRRING ELEMENT ALIGNMENT-

- The USP / NF XV states that the axis of the stirring element must not deviate more than 0.2 mm from the axis of the dissolution vessel which defines centering of stirring shaft to within ±2 mm.
- Studies indicant that significant increase in dissolution rate upto 13% occurs if shaft is offset 2-6 mm from the center axis of the flask.
- Tilt in excess of 1.5^0 may increase dissolution rate from 2 to 25%.

3. SAMPLING PROBE POSITION & FILTER-

- 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 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 surface may cause significant error in the dissolution testing.

V. FACTORS RELATING DISSOLUTION TEST PARAMETERS

1. TEMPERATURE-

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

2. DISSOLUTION MEDIUM-

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

  - **Effect of pH**-

  ✓ Weak acids, dissoln rate increases with increase in pH whereas for weak bases, increase with decrease in pH.

  - **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

    1. continous flow method where fresh solvent is pumped continuously into dissoln flask at a fixed flow rate while maintaining a constant volume.
    2. use of non-ionic surfactant in conc. above CMC.
    3. use of alcoholic solution (10-30%).

  - **Deaeration of dissolution medium-**

- ✓ 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.