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RR COLLEGE OF PHARMACY

BIOPHARMACEUTICS AND PHARMACOKINETICS

BIOAVAILABILITY ENHANCEMENT METHODS

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Enhancement of bioavailability:

Bioavailability enhancement through following methods. They are ,

1. Enhancement of drug solubility or dissolution rate.
2. Enhancement of drug permeability Enhancement of drug stability
3. Enhancement of gastrointestinal retention

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A). ENHANCEMENT OF DRUG SOLUBILITY OR DISSOLUTION RATE:

1. Micronization
2. Nanonisation
3. Supercritical fluid recrystallization
4. Spray freezing into liquid(SFL)
5. Evaporative precipitation into aqueous solution (EPAS)
6. Use of surfactant
7. Use of salt forms
8. Use of precipitation inhibitors

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9. Alteration of pH of drug microenvironment
10. Use of amorphs , anhydrates, solvates and metastable polymorphs
11. Solvent deposition
12. Precipitation
13. Selective absorption on insoluble carriers
14. Solid solutions
15. Eutectic mixtures
16. Solid dispersions
17. Molecular encapsulation with cyclodextrins

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B). **ENHANCEMENT OF DRUG PERMEABILITY:**

1. Lipid technologies
2. Ion pairing
3. Penetration enhancers

C). **ENHANCEMENT OF DRUG STABILITY**:

1. Enteric coating
2. Complexation
3. Use of metabolism inhibitors

D) **ENHANCEMENT OF GASTROINTESTINAL RETENTION:**

1. Incresed contact with epithelial surface
2. Prolonged residence time in the stomach
3. Delaying intestinal transit

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A). ENHANCEMENT OF DRUG SOLUBILITY OR DISSOLUTION RATE:

1. Micronization :

- Reduce the size of solid drug particle to 1-10 microns
- It also called as micro milling
- Particle size Is reduced by Spray drying or by use of air attrition methods (fluid energy or jet mill).
- Ex: Griseofulvin and several steroidal and sulpha drugs

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2) Nanonisation :

- The drug powder is converted to nano crystals of sizes 200-600nm.
- E.g. amphotericin B
- Dispersion of drug nano crystals in a liquid (water) called as nano suspension .
- There are 3 technologies use to prepare nano particles:
- Pearl milling
- Homogenisation in water (wet milling as in a colloid mill).
- Homogenisation in non aqueous media or in water with water miscible liquid

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3) Supercritical fluid recrystallization :

•Supercritical fluids are fluids whose temperature & pressure are greater than its critical temperature(Tc) & critical pressure (Tp) , allowing it to assume the properties of both a liquid and gas.

•At near critical temperatures, SCFs are highly compressible, allowing moderate changes in pressure to greatly alter the density & mass transport characteristics of a fluid that largely determine its solvent power.

•Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle sizes

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4)Spray freezing into liquid(SFL) :

•This technique involves atomizing an aqueous, organic, aqueous-organic cosolvent solution, aqueous-organic emulsion or suspension containing a drug & pharmaceutical excipients directly into a compressed gas(CO2,helium,propane,ethane) or the cryogenic liquids(nitrogen, organ or hydrofluoroethers).

•The frozen particles are then lyophilized to obtain dry and free flowing micronized powders use of acetonitrile as the solvent increases drug loading &decreases the drying time for lyophilization . The dissolution rate is remarkably enhanced from the SFL powder containing amorphous nanostructured aggregates with high surface area & excellent wettability

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5)Evaporative precipitation into aqueous solution (EPAS) :

•The EPAS process utilizes rapid phase separation to nucleate & grow nanoparticles & microparticles of lipophilic drugs.

•The drug is first dissolved in a low boiling point organic solvent.

•This solution is pumped through a tube where it is heated under pressure to a temperature above the solvents boiling point &then sprayed through a fine atomizing nozzle into a heated aqueous solution.

•Surfactants are added to the organic solution &the aqueous solution to optimize particle formation &stabilization. In EPAS, the surfactant migrates to the drug-water interface during particle formation and the hydrophilic segment is oriented towards the aqueous continuous phase.

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The hydrophilic stabilizer on the surface inhibits crystallization of the growing particles & therefore facilitates dissolution rate

6) Use of surfactant :

•Surfactants are very useful as absorption enhancers and enhance both dissolution rate & permeability of drug.

•They enhance dissolution rate primarily by promoting wetting & penetration of dissolution fluid into the solid drug particles.

•They are generally used in concentration below their critical micelle concentration (CMC) values since above CMC, the drug entrapped in the micelle structure fails to partition in the dissolution fluid.

•Nonionic surfactants like polysorbates

•Steroids like spiranolactones

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7) Use of salt forms :

•Salts have improved solubility & dissolution charecteristics in comparison to the original drug.

•It is generally accepted that a minimum difference of 3 units between the pKa value of the group& that of its counterion is required to form stable salts.

•E.g. alkali metal salts of acidic drugs like penicillins &strong acid salts of basic drugs like atropine

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8) Use of precipitation inhibitors:

•A significant increase in free drug concentration above equilibrium solubility results in supersaturation, which can lead to drug precipitation or crystallization.

•This can be prevented by use of inert polymers such as HPMC, PVP, PVA, PEG, etc.

•Which act by one or more mechanisms-

•In the crystallization rate of drugs

•Provide a steric barrier to drug molecules & inhibit crystallization through specific intermolecular interactions on growing crystal surfaces.

•Adsorbs onto faces of host crystals, reduce the crystal growth rate of the host and produce smaller crystalsc the viscosity of crystallization medium there by reducing

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9)Alteration of pH of drug microenvironment :

•Insitu salt formation

•Addition of buffersto the formulation

•E.g. Buffered aspirin tablets.

10).Use of amorphs, anhydrates, solvates and metastable polymorphs:

•Depending upon the internal structure of the solid drug, selection of proper form of drug with greater solubility is important.

•In general, amorphs are more soluble than metastable polymorphs, anhydrates are more soluble than hydrates &solvates are more soluble than non-solvates.

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12) Precipitation :

•The poorly aqueous soluble drugs such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nanosize particles. The product so prepared is also called as hydrosol

13) Selective absorption on insoluble carriers :

•A highly active adsorbent such as the inorganic clays like bentonite can enhance the dissolution rate of poorly water soluble drugs like griseofulvin, indomethacin & prednisone by maintaining the concentration gradient at its maximum.

•The two reasons suggested for the rapid release of drugs from the surface of clays are- the weak physical bonding between the adsorbate & the adsorbent & the hydration & swelling of clay in the aqueous media.

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14).Solid solutions :

•A solid solute molecularly dispersed in a solid solvent. Since the two components crystallize together in a homogeneous one phase system, solid solutions are also called as molecular dispersions or mixed crystals.

•Because of reduction in particle size to the molecular level, solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersion.

•They are generally prepared by fusion method where by a physical mixture of solute and solvent are melted together followed by rapid solidification.

•Such systems, prepared by fusion, are often called as melts

•e.g. : griseofulvin - succinic acid

•The griseofulvin from such solid solution dissolves 6-7 times faster than pure griseofulvin

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15).Eutectic mixtures :

•These systems are also prepared by fusion method .

•A phase diagram of two-component system is shown in diagram. When the eutectic mixture is exposed to water, the soluble carrier dissolves leaving the drug in a microcrystalline state which solubilizes rapidly.

•Examples

• paracetamol -urea,

•griseofulvin -urea,

•griseofulvin-succinic acid , etc

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16).SOLID DISPERSION:

•The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the

1. Hot melt method.
2. Solvent evaporation method.
3. Hot melt extrusion method.

- These are generally prepared by solvent or co-precipitation method.
- Where by both the guest solute & the solid carrier solvent are dissolved in a common volatile liquid solvent such as alcohol

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•The liquid solvent is removed by evaporation under reduced pressure or by freeze drying which results in amorphous precipitation of guest in a crystalline carrier.

•The basic difference between the solid solutions/eutectics is that the drug is precipitated out in an amorphous form in the former as opposed to crystalline form in the latter.

•E.g. amorphous sulphathiazole in crystalline urea.

•Such dispersions are often called as co-evaporates or co-precipitates.

•With glassy materials, the dispersions formed are called as glass dispersions or glass suspensions

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17). Molecular encapsulation with Cyclodextrins:

•The beta and gamma- cyclodextrins and several of their derivatives are unique in having the ability to form molecular inclusion complexes with hydrophobic drugs having poor aqueous solubility.

•These bucket shaped oligosaccharides produced from starch are versatile in having a hydrophobic cavity of size suitable enough to accommodate the lipophillic drugs as guests, the outside of the host molecule is relatively hydrophillic.

•Thus, the molecularly encapsulated drug has greatly improved aqueous solubility & dissolution rate.

•There are several examples of drugs with improved bioavailability due to such a phenomenon- thiazide diuretics, barbiturates, benzodiazepines & number of NSAIDs

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