•Formulation developing during early drug discovery and lead optimization, involve several challenges including limited drug supply, the need for rapid turnaround, limited development time.

Its also desirable to develop initial formulation that will be representative of final commercial formulation.

Nanoparticles offer a unique platform for the formulation of poorly soluble drug such formulation can be injected (IV, SC, IM), as well as administered through routes, such as oral, ocular and inhalation.

-Rapid formulation and identification of an appropriate formulation are crucial for an accurate assessment of compound in a drug discovery setting. The challenges involved with formulation during this stage are, the limited availability of compound, limited drug characterization data and a need for rapid turnaround.

Given these challenges, screening technologies are required to be versatile, robust and scalable.

- Two approaches can be taken to formulate compounds in this stage of discovery:

a- Rapid formulation development wherein compound are formulated rapidly for in vivo testing, not necessarily considering the commercial viability of the formulation (ie. the powder in a bottle approach).

b- Robust and thorough formulation development, wherein effort is made to make the formulation commercially viable.

- The rapid formulation development is desirable in situations involving screening of multiple candidates with a limited assigned probability of success.

A more detailed formulation development is desired early on especially in situation involving time constraints and for leads with higher probability of success. There is a further desire to converge these two approaches, by the development and use of rapid formulation

techniques that are scalable and commercially viable.

-The drug discovery process:

A biopharmaceutical classification system (BCS) has been developed to categories hit compound, based on their aqueous solubility and GI permeability.

Class 1: High permeability, High solubility

Eg: propranolol, diltiazem, verapamil

- These compounds are well absorbed and their absorption rate is usually higher than excretion.

Class 2: High Permeability, Low solubility

Eg: Glibenclamide, mefenamic acid

-The bioavailability of those product is limited by their solvation rate.

Class 3: Low permeability, High solubility

Eg: Captopril, cimetidine

The absorption is limited by the permeation rate

but the drug is solvated very fast. If the formulation does not change the permeability or gastro intestinal duration time, the class 1 criteria can be applied.

Class 4: Low permeability, Low Solubility

Eg: Taxol, hydrochlorothiazide

-Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and high solubility (class 1) are generally easiest to formulate - a simple powder for reconstitution is sufficient or early studies. However, poorly soluble and or poorly permeable compounds pose a significant challenge. Such compounds often require an array of technologies to provide a viable formulation Early screening dose not differentiate compounds based on their solubility, therefore there is an increasing bias toward lipophilic (and consequently poorly soluble) drugs entering and processing through the development pipeline.

Furthermore, retrospective analysis suggests that drug discovery methodologies are biases towards low potency compounds, with a typical potency in the range of 1mg/kg.

Formulation tools for drug development:

Two of the most important per formulation factor that are considered during compound screening are Solubility and permeability Both these factors directly affect the oral bioavailability of the compound. Solubility of the drugs is estimated in silico based on structure and can be experimentally verified using techniques such as Laser Nephelometry.

Similarly, permeability can be estimated from several semi-empirical models [such as those based on quantitative-SARs (QSAR).

Additionally, software programs are now available to estimate intestinal absorption. Compounds that are identified as poorly soluble and/or show

poor bioavailability might require additional formulation expertise at the development stage, as discussed in subsequent sections. However, irrational decisions based on these factors can lead to elimination of compounds that might otherwise be promising.

□ The term solid dispersion defined as the dispersion of one or more active ingredients (hydrophobic) in an inert carrier or matrix (hydrophilic) at solid stated by the melting (fusion), solvent or melting-solvent method.

Class	Solubility	Permeability	Absorption Pattern	Rate-limiting Step in Absorption
I	High	High	Well absorbed	Gastric emptying
II	Low	High	Variable	Dissolution
III	High	Low	Variable	Permeability
IV	Low	Low	Poorly absorbed	Case by case

oEnabling formulation technologies:

Novel enabling technologies are desired for challenging drugs where conventional technologies do not provide a viable solution. Through drug delivery research, several enabling technologies are now becoming available to formulate compounds that are poorly soluble. At the same time, formulation scientists can not merely depend on these technologies to assist development at a later stage. The use of these technologies and subsequent experimental demonstration of this are crucial elements required in lead optimization. Hence there is a need for such enabling technologies to be tested at small scales in a drug discovery setting.

oSolid dispersions.

Solid dispersion technologies involve stabili-

zation of the drug in its amorphous form, within a carrier matrix. The amorphous form allows faster dissolution of the drug and is particularly promising for orally administered drug (because of the wider choices of carrier matrices).

- Typical carrier used for this technology include water soluble polymer, such as polyvinyl pyrrolidone, polyethylene glycol.
- The drug carrier screening tool can be used in conjunction with miniaturized proceeding equipment (such as the micro-spray dryer developed by particle and coating technologies) to develop and screen solid dispersion formulation of poorly soluble drugs.

- Solubilizing agent:

Complexation using carriers such as

Cyclodextrin is another approach that can be used for solubilization and screening of poorly soluble compounds.

. 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 are versatile in having a hydrophobic cavity of size suitable enough to accommodate the lipophilic drugs as guests; the outside of the host molecule is relatively hydrophilic.

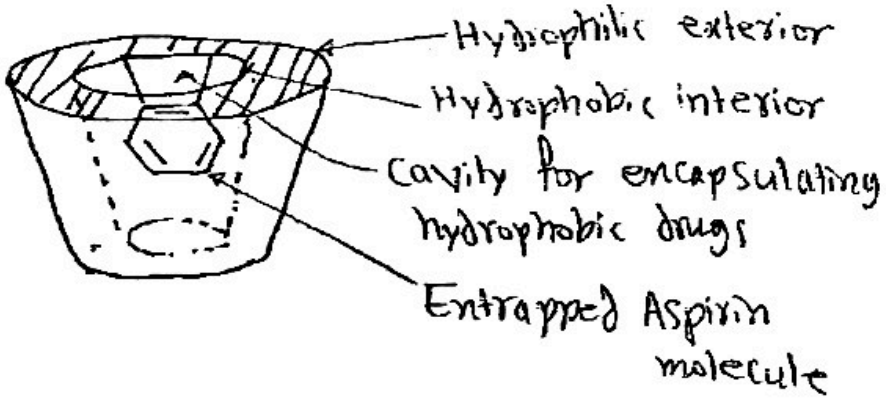

Fig. Functional and structural feature of a cyclodextrin molecule showing an encapsulated drug.

- Thus, the molecularly encapsulated drug has greatly improved aqueous solubility and dissolution rate.

- limitations:

1- Several naturally occuring and commercially available cyclodextrins have exhibited toxicity.

2. Cyclodextrins require the drug to have specific molecular properties to efficiently form a complex.

□ Lipid-based complexation:

- Complexation using lipids is another strategy that can be adopted for poorly soluble drugs. Various complexes can be formed including liposome, micelles, cubosomes and solid lipid nanoparticle.

- Lipid can also be used in developing

Self emulsifying drug delivery system (SEDDS), lipid vesicle, particularly liposomes, have been used extensively for targeting of chemotherapeutic drugs to tumours.

- Liposomes provide an additional benefit of being applicable for both water soluble drugs (whereby the drug is encapsulated in the lipid bilayers. Finally, for oral applications, lipid vesicles might serve as permeation enhancers, increasing the bioavailability of drugs. Furthermore the presence of high amounts of lipid might provide an analytical challenge in identifying the effect of the drug versus the excipient.

- **Particle size reduction:**

- Poorly soluble drugs can be formulated as nanoparticles with high surface area, which

enhances dissolution rates in accordance with Noyes-Whitney equation:

$$\frac{dQ}{dt} = \frac{D}{h} S(C_s - C_g)$$

C_s ... concentration of drug in bulk of the soln

C_g ... in the stagnant layer

h ... thickness of the stagnant layer

where, the rate of dissolution ($\frac{dQ}{dt}$) is proportional to the diffusion coefficient of the drug (D), the available surface area(S) and the difference b/w Saturation solubility of the drug in the boundary layer (C_s) and concentration of drug in the bulk fluid (C_g).

oParticle size reduction can be achieved mainly by two of processes:

1. Particle formation processes (microprecipitation, chemical synthesis, complexation).
2. Particle comminution (size reduction) processes: homogenization, milling, grinding.

The two types of processes can also be combined for a synergistic effect as adopted by the Nanoedge technology platform. A particle formation step (micro precipitation) is employed just before a particle comminution step in this platform; a particle formation step is designed to produce customized, friable particles that are amenable to comminution via high pressure homogenization.

Besides enhanced dissolution, nanoparticles offer the potential for passive or active targeting of drugs. When administered intravenously, nanoparticles have a tendency to be taken up by the reticuloendothelial system (RES). This provides a potential for targeting for macrophage related disorders.

Nanoparticles can be coated with hydrophilic polymers, such as polyethylene glycol, to prevent

RES uptake. Such particles have a tendency to circulate for longer periods of time, and are typically taken up by tumour cells via the enhanced permeation and retention (EPR) effect. Furthermore, nanoparticles can be coated with specific functional groups for active targeting. For example, thiamine coated nanoparticles demonstrated preferential uptake in the brain, via the blood-brain-barrier thiamine transporters. Nanoparticles can also be administered via multiple routes of administration, as a solid or a suspension.

Thus a single formulation can lead to multiple dosing options early in the development program.

•Nanoparticles further provide clinical benefits including enhanced bioavailability,

reduced fed-fasted ratio (for oral application). Given these factors it is anticipated that nanoparticles could offer potential solution for expending the lead selection and the drug development process.

Route of administration	Potential benefit
oral	Rapid onset, reduced fed-fasted ratio, improved bioavailability
IV	Rapid dissolution, tissue targeting
SC/IM	Rapid onset, reduced tissue irritation, Higher bioavailability
Inhalation	Higher bioavailability ,more consistent dosing
ocular	Higher bioavailability more consistent dosing

Rapid formulation screening:

Several platforms have been developed to provide rapid formulation screening. These platform involve a combination of one or more traditional and novel enabling technologies.

Poorly soluble drugs(solubility less than 500nm)are processed rapidly(& in small quantities)as nan suspensions that are stabilize either in suspension or frozen or lyophilized. The suspension is tested in animals for efficacy & the process is repeated iteratively till the hit compounds with desired efficacy is identified.

More rigorous testing can be performed at this stage to assess the formulation before scale up.

It is anticipated that other versatile technologies with rapid screening functionalities might also be used in a similar fashion.