Formulation approach to enhance the absorption of each BCS

BCS	Absorption rate control	Formulation approaches for oral administration
Class 1	Gastric emptying	Can easily be formulated as tablets or capsules
Class 2	Dissolution	Particle size reduction (e.g., formation of microparticles or nanoparticles), solid dispersions, salt formation, addition of surfactants, self-emulsifying systems, liquid capsules, complexation
Class 3	Permeability	Addition of permeation enhancers, efflux inhibitors
Class 4	Dissolution and Permeability	Combination of Class II and III approaches

The advantages of using excipients on drug product performance

1. Improve the manufacturability of the dosage form.
2. Stabilize the drug against degradation.
3. Decrease gastric irritation.
4. Control the rate of drug absorption from the absorption site.
5. Increase drug bioavailability.

The mechanisms by which excipients affect the dissolution kinetics of the drug

1. Altering the medium in which the drug is dissolving

- Suspending agents can increase the viscosity of the drug vehicle and thereby diminish the rate of drug dissolution from suspensions.
- Tablet lubricants, such as magnesium stearate, may repel water and reduce dissolution when used in large quantities (**Figure 14**).

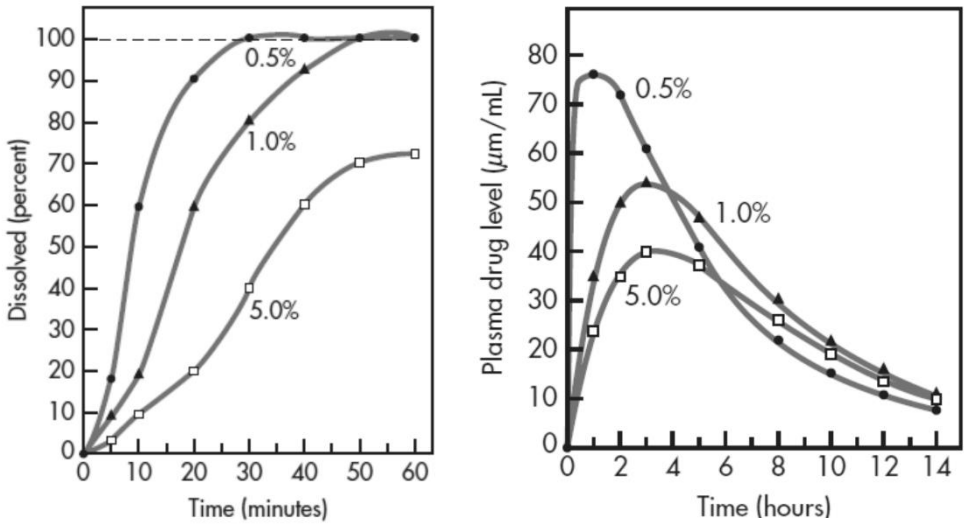


Figure 14. The effect of adding different concentrations of magnesium stearate to a tablet formulation on the dissolution profile (left panel) and plasma conc.-time profile (right panel).

- Coatings, particularly shellac, will crosslink upon aging and decrease the dissolution rate.
- Surfactants: low concentrations of surfactants decrease the surface tension and increase the rate of drug dissolution, whereas higher surfactant concentrations tend to form micelles with the drug and thus decrease the dissolution rate.
- Some excipients, such as sodium bicarbonate, may change the pH of the medium surrounding the active drug substance.

Example: Aspirin, a weak acid when formulated with sodium bicarbonate, will form a water-soluble salt in an alkaline medium, in which the drug rapidly dissolves. The term for this process is ***dissolution in a reactive medium***.

2. **Directly in interaction with the drug to form a water-soluble or water-insoluble complex.**

For example, if tetracycline is formulated with calcium carbonate, an insoluble complex of calcium tetracycline is formed that has a slow rate of dissolution and poor absorption.

Effect of excipients on the pharmacokinetic parameters of oral drug products

Excipients	**Example**	k_a	t_{max}	**AUC**
Disintegrants	Avicel, Explotab	↑	↓	↑/−
Lubricants	Talc, hydrogenated vegetable oil	↓	↑	↓/−
Coating agent	Hydroxypropylmethyl cellulose	–	–	–
Enteric coat	Cellulose acetate phthalate	↓	↑	↓/−
Sustained-release agents	• Methylcellulose, ethylcellulose • Castorwax, Carbowax (waxy agents) • Veegum, Keltrol (gum/viscous)	↓	↑	↓/−

DISSOLUTION AND DRUG RELEASE TESTING

Dissolution and drug release tests are *in vitro* tests that measure the rate and extent of dissolution or release of the drug substance from a drug product, usually in an aqueous medium under specified conditions.

Purpose of Dissolution and Drug Release Tests

1. Formulation development and selection
2. Confirmation of batch-to-batch reproducibility
3. Establish drug product stability (demonstrate that the product performs consistently throughout its use period or shelflife).

4. Establish *in vivo–in vitro* correlations (IVIVC)
5. Evaluate the biopharmaceutic implications of a product change, rather than to require a bioequivalence study (SUPAC—scale-up and postapproval changes).

The choice of apparatus and dissolution medium is based on:

1. The physicochemical characteristics of the drug (including solubility, stability).
2. The type of formulation (such as immediate release, enteric coated, extended release, rapidly dissolving, etc).

Apparatus factors that affect the rate and extent of dissolution

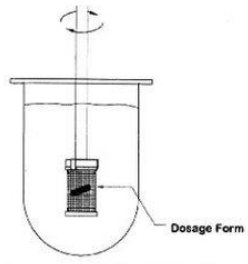
1. The size and shape of the dissolution vessel.
2. The amount of agitation and the nature of the stirrer affect hydrodynamics of the system.
3. The temperature of the dissolution medium (most dissolution tests are performed at 37°C. However, for transdermal drug products, the recommended temperature is 32°C).
4. The nature of the dissolution medium.

***Sink conditions**:* the quantity of medium used should not be less than 3 times that needed to form a saturated solution of the drug substance

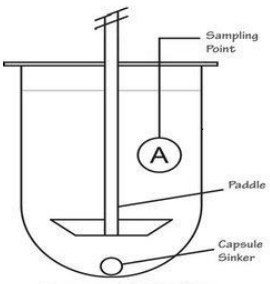
USP-NF Dissolution Apparatus

Apparatus	Name	Agitation Method	Drug Product	Notes
Apparatus 1	Rotating basket	Rotating stirrer	Tablets, capsules	rotating speed 100-150 rpm formulation may clog to mesh
Apparatus 2	Paddle	Rotating stirrer	Tablets, capsules, modified drug products, suspensions	50 - 75 rpm for solid dosage form 25 rpm for oral suspensions. May require the use of sinker to prevent floating of tab or capsules
Apparatus 3	Reciprocating cylinder	Reciprocation	Extended-release drug products	Flat bottom The agitation rate is generally 5–30 dpm (dips per minute) The media can be changed easily.
Apparatus 4	Flow cell	Fluid movement	Drug products containing low water-soluble drugs	Flow rate ranges from 4 to 32 mL/min Maintains sink condition for dissolution

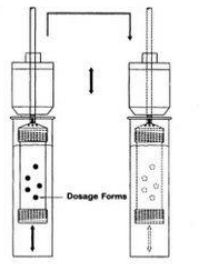
Apparatus 5	Paddle over disk	Rotating stirrer	Transdermal drug products	Modification of USP II apparatus stainless steel disk to hold the transdermal system at the bottom of the vessel
Apparatus 6	Cylinder	Rotating stirrer	Transdermal drug products	Modification of USP I apparatus Samples are hold in cuprophan
Apparatus 7	Reciprocating disk	Reciprocation	Extended-release drug products	Samples are hold in disk-shaped holders using cuprophan supports



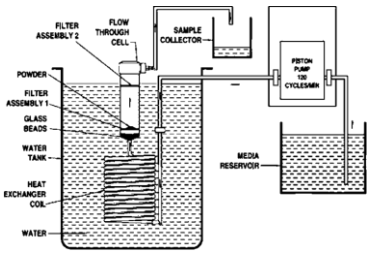
Apparatus I: Rotating basket

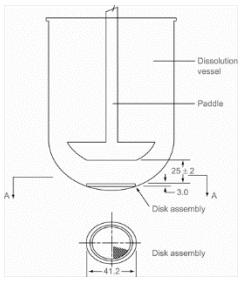


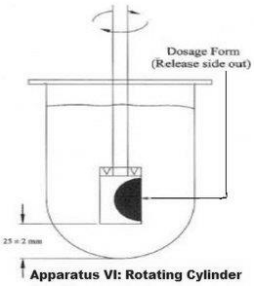
Apparatus II: Paddle



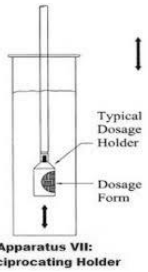
Apparatus III
Reciprocating cylinder







Apparatus VI: Rotating Cylinder



Apparatus VII:
Reciprocating Holder