tablets & capsules

what are the usual excipients in a tablet?

- **Fillers/diluents** fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use (i.e. minimum measurable quantity). A good filler must be inert, compatible with the other components, non-hygroscopic (doesn't attract water), soluble, inexpensive, compactable, and preferably tasteless/pleasant.
  Examples: lactose, microcrystalline cellulose dicalcium phosphate, sucrose, mannitol
- **Binder** is added to help hold the ingredients in a tablet together and give it strength. They ensure that tablets and granules can be formed with required mechanical strength during the manufacturing process.
  Examples: povidone, gelatin, methylcellulose, starch
- **Glidant** is a substance that is added to a powder to improve its flowability. A glidant will only work at a certain range of concentrations. Above a certain concentration, the glidant will in fact function to inhibit flowability. In tablet manufacturing, glidants are usually added just prior to compression. A glidant's effect is due to a counter-action to factors resulting in poor flowability of powders. For instance, correcting surface irregularity, reducing interparticular friction, and decreasing surface charge. The result is a decrease in the angle of repose which is an indication of an enhanced powder's flowability. Glidants are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction.
  Examples: magnesium carbonate, silicon dioxide, talc
- **Lubricants** help the tablets, once pressed, to be more easily ejected from the die. Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine by lowering friction.
  Examples: talc, silica, magnesium stearate
- **Disintegrants** aid tablet dispersion once swallowed, releasing the API for absorption. Some binders are also excellent disintegrants. They expand and dissolve when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption.
  Examples: crospovidione, starch, sodium starch glycolate
- **Preservatives** are used in pharmaceutical formulations as antimicrobials.
  Examples: parabens, sorbic acid
- **Plasticizers/dispersants** are additives that increase the plasticity or fluidity of the material to which they are added.
- **Color/flavor** are for cosmetic purposes and to make the tablet easier to take.
  Examples: dyes, lakes, vanillin, flavors, aspartame (sweetener)

what are the usual excipients in gelatin capsules?

- **Vehicle**s dissolve and solubilize drugs.
  Example: soybean oil, polyethylene glycols
- **Solubility adjuvants** enhance drug solubility and make them more hydrophilic.
  Examples: surfactants, alcohols, glycols
- **Suspending/viscosity agents** help suspend insoluble drugs.
  Examples: waxes, gums
- **Gelatin**

Check out http://www.rjengineering.com/process.htm to see how HARD gelatin capsules are manufactured
Check out http://www.kwangdah.com/kde-300.htm to see how SOFT gelatin capsules are manufactured

what are some problems associated with gelatin capsules?

Gelatin capsules require more specialized equipment and therefore cost more to manufacture, they are especially susceptible to moisture, have aldehyde reaction incompatibilities, and many religions have dietary restrictions that prevent them from using the capsules since gelatin is made from the bones and skins of cows and pigs.

what are some special excipients with specific functions?

Enteric coated tablets: dissolve in alkaline and not acidic pH, allowing them to reach a site of action in the intestines
Controlled release tablets: hydroxypropylcellulose in tablet core, waxes
Chewable tablets: mannitol
Effervescent tablets: citric acid, sodium bicarbonate, foil pouches
Gelatin capsules: aldehyde reaction incompatibility

what dosage forms are easier to formulate?

From easiest to most difficult in terms of cost/efficiency:

1. Direct compression without coating
2. Granulated
3. Granulated with adjuvants
4. Granulation with additional processes like micronization and coating
5. Gelatin capsules (special equipment needed, increases cost of production)
6. Granules for reconstitution

what is the main test a drug undergoes to evaluate its specification?

Dissolution! Each drug has a dissolution profile that reveals what percentage of a drug is dissolved with time. It is important for development, clinical testing, FDA submission, and more. It is usually tested through a very simple apparatus: a container with a paddle that spins. The aqueous medium inside the container that the drug is dissolved in is made up of water, a buffer, surfactant to solubilize the drug, and if necessary, a semipolar solvent to increase solubility (water + ethanol).

how is bioavailability measured?

When comparing blood levels, they look at the AUC, Tmax, and Cmax as seen on a serum concentration vs. time graph.

what is the coating composed of?

Each coating will have a solvent, polymer, and plasticizer.
Coating formulation includes the subcoat, color coat, gloss coat, and printing.

what is the purpose of coating a tablet?

To enhance the appearance, hide the bad taste, make it easier to swallow, aid in drug stability to extend shelf life (e.g. protection from light, moisture, oxidation, and stomach acid), reduce stomach irritation, allow identification through printing, and for controlled release.
If the active ingredient of a tablet is sensitive to acid or is an irritant to the stomach lining, an enteric coating can be used, which is resistant to stomach acid and dissolves in the alkaline environment of the intestines.
Coatings are often chosen to control the rate of dissolution of the drug in the gastrointestinal tract. Some drugs will be absorbed better at different points in the digestive system.

what are important considerations when manufacturing a tablet?

It is important that all ingredients be fairly dry, powdered or granular, somewhat uniform in particle size, and freely flowing. Mixed particle sized powders can segregate during manufacturing operations, which can result in tablets with poor drug or active pharmaceutical ingredient (API) content uniformity. Content uniformity ensures that the same API dose is delivered with each tablet.

describe the different steps of the manufacture process:

1. **Particle size reduction**
    a. Milling/comminution
    b. Starve Mill
    c. Choke Mill
    d. Feed rate is important
2. **Granulating/massing**
    a. The most important process!
    b. Ingredients must be granulated prior to compression to assure an even distribution of the active compound in the final tablet. Two basic techniques are used to granulate powders for compression into a tablet: wet granulation and dry granulation.
    c. **Wet granulation** is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable.
    d. **Low shear wet granulation** processes use very simple mixing equipment, and can take a considerable time to achieve a uniformly mixed state. **High shear wet granulation** processes use equipment that mixes the powder and liquid at a very fast rate, and thus speeds up the manufacturing process. Fluid bed granulation is a multiple-step wet granulation process performed in the same vessel to pre-heat, granulate, and dry the powders. It is used because it allows close control of the granulation process.
    e. **Dry granulation** processes create granules by light compaction of the powder blend under low pressures. The compacts so-formed are broken up gently to produce granules (agglomerates). This process is often used when the product to be granulated is sensitive to moisture and heat. It is simpler and cheaper than wet granulation. Dry granulation often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet. Dry granulation requires drugs or excipients with cohesive properties, and a 'dry binder' may need to be added to the formulation to facilitate the formation of granules.
    f. Powders that can be mixed well do not require granulation and can be compressed into tablets through **direct compression.**
    g. Problems: overwet, underwet, overmass, ratio of binder/liquid to surface area
3. **Drying**
    a. Can use either a fluidized bed dryer, tray driver, or a microwave
    b. Problems: overwet, underwet, attrition (erosion by friction), and differences in sampling
4. **Mixing/blending by lubrication**
    a. Can use either a V-shaped mixer or a double cone mixer
    b. Problems: fill volume of blender, attrition, over blending, under blending
5. **Sizing/milling/separating**
    a. Segregate by the size, shape, density, vibration, air flow, or sampling
6. **Compressing**
    a. Characterized by the weight, hardness, thickness, friability, and disintegration
    b. Problems: flow, segregation, excess force, capping, picking, sticking, chipping
7. **Coating**
    a. The purpose is to protect against dissolution and to enhance appearance
    b. Problems: overwet, underwet, twinning, bridging, picking, peeling, roughness, and breakage
8. **Printing**

how are tablets formed and what are some problems encountered?

Watch how to make a tablet! http://en.wikipedia.org/wiki/File:Tablet_press_animation.gif

First, the powder is filled into the die from above. The mass of powder is determined by the position of the lower punch in the die, the cross-sectional area of the die, and the powder density. At this stage, adjustments to the tablet weight are normally made by repositioning the lower punch. After die filling, the upper punch is lowered into the die and the powder is compressed. Finally, the upper punch is pulled up and out of the die (decompression), and the tablet is

ejected from the die by lifting the lower punch until its upper surface is flush with the top face of the die. This process is simply repeated many times to manufacture multiple tablets.

Common problems encountered during tablet manufacturing operations include:

- Poor weight uniformity, usually caused by uneven powder flow into the die
- Poor content uniformity, caused by uneven distribution of the API in the tableting blend
- Sticking of the powder blend to the tablet tooling, due to inadequate lubrication, worn or dirty tooling, and sub-optimal material properties
- Capping, lamination or chipping; such mechanical failure is due to improper formulation design or faulty equipment operation

what are the differences of excipients among the dosage forms?

Granules/sachets have a lot of diluent/filler, a dispersant/plasticizer, but no disintegrant
Tablets and capsules don't need a dispersant but do have a disintegrant
Chewables and buccal tablets don't need a disintegrant
Effervescent tablets need acid base excipients

what are some problems encountered with excipients?

They may undergo chemical and physical reactions with the other components, contain some moisture, cause manufacturing problems, support microbial growth, and absorb moisture, thereby losing some functionality.

what is process analytical technology? (pat)

Defined by the FDA as a mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (**CPP**) which affect Critical Quality Attributes (**CQA**).
It regulates parameters for drying, milling, granulating, compressing, and coating.

what is quality by design? (qbd)

QbD is a concept under the belief that quality could be planned, and that most quality crises and problems relate to the way in which quality was planned in the first place. The FDA has adopted QbD as a vehicle for the transformation of how drugs are discovered, developed, and commercially manufactured. The focus of this concept is that quality should be built into a product with a thorough understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks.

Two ways to characterize QbD is by looking at

1. Quality Target Product Profile (**QTPP**) which describes the ideal profile of the product that is to be manufactured
2. Critical Quality Attributes (**CQA**) which describes the important characteristics that the product needs to have to ensure quality

what and how are products tested?

The components that are tested are the API, excipients, packaging, and product. These all have certain specifications that need to be met, which include the potency, uniformity, degradation, moisture level, dissolution rate, microbial, description, identification, and hardness (if a chewable tablet).

To test tablets, they take a number of tablets (say 10 to 20), grind them up, sample it, and do an assay. For whatever quality they are testing for, it needs to be within an acceptable range (say 90-110% of the ideal), which can also be described as the RSD ("relative standard deviation") as being within a certain percentage of error (e.g. +/- 5%).

what is good manufacturing practice? (gmp)

It outlines the aspects of production and testing that can impact the quality of a product. GMP guidelines are not prescriptive instructions on how to manufacture products. They are a series of general principles that must be observed during manufacturing. When a company is setting up its quality program and manufacturing process, there may be many ways it can fulfill GMP requirements. It is the company's responsibility to determine the most effective and efficient quality process.