PHARMACY INDIA

COMMON INTERVIEW QUESTIONS & ANSWERS

FOR R&D/ QC/ QA/ PRODUCTION

PHARMA GRADUATES & POST-GRADUATES

Question 1: What is pH?

The pH is defined as the negative $\log_{10}$ of the hydrogen ion concentration expressed in mol/L. A negative logarithmic scale is used because the numbers are all less than 1, and vary over a wide range. Since the pH is the negative logarithm of the hydrogen ion concentration, low pH numbers, e.g. pH 6.2, indicate relatively high hydrogen ion concentrations, i.e. an acidic solution. High pH numbers, e.g. pH 7.8, represent lower hydrogen ion concentrations, i.e. alkaline solutions. Because the pH scale is logarithmic to the base 10, a 1-unit change in pH represents a 10-fold change in hydrogen ion concentration.

The normal pH range in human tissues is 7.36–7.44. Although a neutral pH (hydrogen ion concentration equals hydroxyl ion concentration) at 20°C has the value 7.4, water dissociates more at physiological temperatures, and a neutral pH at 37°C has the value 6.8. Therefore, body fluids are mildly alkaline (the higher the pH number, the lower the hydrogen ion concentration).

Question 2: What is pka and Buffer Capacity?

- The pKa value is one method used to indicate the strength of an acid.
- pKa is the negative log of the acid dissociation constant or Ka value.
- A lower pKa value indicates a stronger acid. That is, the lower value indicates the acid more fully dissociates in water.

pKa and Buffer Capacity

In addition to using pKa to gauge the strength of an acid, it may be used to select buffers. This is possible because of the relationship between pKa and pH:

pH = pKa + log10([A-]/[AH])

Where the square brackets are used to indicate the concentrations of the acid and its conjugate base.

The equation may be rewritten as:

Ka/[H+] = [A-]/[AH]

This shows that pKa and pH are equal when half of the acid has dissociated. The buffering capacity of a species or its ability to maintain pH of a solution is highest when the pKa and pH values are close. So, when selecting a buffer, the best choice is the one that has a pKa value close to the target pH of the chemical solution.

Question 3: What is log p?

Lipophilicity plays a significant role in **drug** discovery and compound design. The lipophilicity of an organic compound can be described by a partition coefficient, **logP**, which can be defined as the ratio of the concentration of the unionized compound at equilibrium between organic and aqueous phases.

Question 4: What is Solubility?

Solubility indicates the upper concentration a compound reaches in a solution. Solubility is a very important property in drug discovery and development, because concentration affects so many aspects of pharmacology (e.g., structure-activity relationships, efficacy, pharmacokinetics, toxicity). Different compounds vary widely in their solubilities, owing to differences in their structures and properties. Higher solubility is needed for a compound during development than in discovery, owing to toxicity and other studies. Solubility optimization deserves considerable effort. To increase solubility, chemists modify the structure, such as adding ionizable groups, reducing lipophilicity, or reducing molecular weight. Salt forms and formulation are used to enhance the dissolution rate. Solubility varies with the conditions of the solution (e.g., pH, co-solvents, protein) and, thus, among different pharmacological solutions (e.g., in vitro assay media, intestinal lumen, blood).

Question 5: What you get from Orange Book?

Innovator's Leaflet, Patent Number, Patent Code & Exclusivity, RLD status.

Question 6: Where you search literature from?

Sr.No.	WEB SITES	PURPOSE
1	vidal.fr	Composition of innovators
2	luhs.com	Image and information of innovator
3	tsrlinc.com/search3.cfm	BCS classification
4	drugs.com	Information of drug
5	rxlist.com	Innovator and its information
6	Drugbank---homepage	
7	Dissolution.com(By-law)	Send mail for disso problems
8	Drugsearcher.com	
9	Answers.com	Answer
10	Google.com	
11	Orange book	
12	Fda.gov/cder/ogd/	
13	Cder---freedom of information---index---cder---search	
14	Sengpielaudio.com/convForce.htm	Conversion of units
15	Emc.medicines.org.uk/	Europe Innovator Information
16	DailyMed	US Innovator Information
	PATENT SITES	
1	USPTO-Homepage-Patent search 1)Issued patent---QS 2)Published patent---Q.S	US Patents
2	Europian Patent homepage espacenet Homepage	EU Patents
	OTHER PATENT SITES	
1	Pat2pdf	Full Patent Pdf
2	Patentlens	
3	Patentstorm	
4	WIPO	
	BOOK REFERENCES	
1	Merck Index	
2	Martindale	
3	PDR (Physician Desk reference)	
4	Medicine Compendium	
5	Therapeutic Drugs	
6	Handbook Of Excipients	
7	Florey	
	PHARMACOPOEIAS	
1	USP, EP, BP, IP,JP,	

Question 7: What appears on clicking orange book First page?

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Publications	
FAQ	
• **Search by Active Ingredient**	• **Search by Applicant Holder**
• **Search by Proprietary Name**	• **Search by Application Number**
• **Search by Patent**	

Question 8: What will you get after clicking on Search by active ingredient?

Active Ingredient Search Results from "OB_Rx" table for query on

Example: Levonorgestrel.

Appl No	**TE Code**	**RLD**	**Active Ingredient**	**Dosage Form; Route**	**Strength**	**Proprietary Name**	**Applicant**
N021998		Yes	LEVONORGESTREL	TABLET; ORAL	1.5MG	PLAN B ONE-STEP	DURAMED

Question 9: What is TE Code?

Therapeutic equivalent Codes are as follows.

1	There are no known or suspected bioequivalence problems. These are designated	**AA**, **AN**, **AO**, **AP**, or **AT**, depending on the dosage form
2	Actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence.	These are designated **AB**.
3	Drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. Often the problem is with specific dosage forms rather than with the active ingredients	These are designated **BC**, **BD**, **BE**, **BN**, **BP**, **BR**, **BS**, **BT**, **BX,** or **B***.

Question 10: What is NDC Code (National Drug Code)?

Each listed drug product listed is assigned a unique 10-digit, 3-segment number. This number, known as the NDC, identifies the labeler, product, and trade package size.

The first segment, the labeler code, is assigned by the FDA. A labeler is any firm that manufactures (including repackers or relabelers), or distributes (under its own name) the drug.

The second segment, the product code, identifies a specific strength, dosage form, and formulation for a particular firm.

The third segment, the package code, identifies package sizes and types. Both the product and package codes are assigned by the firm.

The NDC Code will be in one of the following configurations: **4-4-2, 5-3-2, or 5-4-1.**

Question 11: What is SBOA (Summary Basis of Approval_& what you get from SBOA Data/FOI.?

The 1996 amendments to the Freedom of Information Act, FOIA, mandate publicly accessible ‘‘electronic reading rooms’’ with FDA FOIA response materials and other information routinely available to the public with electronic search and indexing features. Before submitting an FOIA request, the sponsor should check to see if the information is already available on FDA’s website. (**http://www.fda.gov/foi/foia2.htm**)

Sr No.	Parameters
1)	Clinical Pharmacology & Biopharmaceutics Review clinical Parameters: Cmax, Tmax, AUC, t1/2)
2)	Bio Recommendations
3)	Formula, manufacturing process
4)	API characteristics
5)	Dissolution Media
6)	Compression Parameters.
7)	Detailed Labelling Recommendations,
8)	Stability

Question 12: What are different types of Patents listed in Orange Book?

Patents that are listed in the Orange Book include:

- Patents that claim the active ingredients or ingredients.
- Drug product patents which include formulation-composition patents.
- Use patents for a particular approved indication or method of using the product.

The Bolar amendment to the Drug Price Competition and Patent Term Restoration Act allows a pharmaceutical manufacturer (sponsor) to seek approval from FDA to market a generic drug before the expiration of a patent relating to the brand name drug upon which the generic is based. As part of the ANDA, the sponsor must consider the pertinent patents and provide the results to the FDA. The Act requires patent information to be ¢led with all newly submitted Section 505 drug applications and that no NDA may be approved after September 24, 1984, without the submission of pertinent patent information to the FDA. The ANDA sponsor must provide a certification that, in the opinion of the sponsor and to the best of the sponsor's knowledge with respect to each patent that claims the listed drug, some or all of the following certification may be submitted:

Paragraph I:	that such patent information has not been filed;
Paragraph II:	that such patent has expired;
Paragraph III:	of the date on which such patent will expire, or
Paragraph IV:	that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.

A certification under Paragraph I or II permits the ANDA to be approved immediately, if it is otherwise eligible.

A certification under Paragraph III indicates that the ANDA may be approved on the patent expiration date.

If the Orange Book lists one or more unexpired patents, the sponsor of The ANDA who seeks effective approval prior to the patent's expiration must either:

- Challenge the listing of the patent (e.g., file a Paragraph IV Certification that the patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product).
- File a statement that the application for use is not claimed in the listed patent.

Question 13: What is Dissolution?

Dissolution rate may be defined as amount of drug substance that goes in the solution per unit time under standard conditions of liquid/solid interface, temperature and solvent composition. It can be considered as a specific type of certain heterogeneous reaction in which a mass transfer results as a net effect between escape and deposition of solute molecules at a solid surface.

IMPORTANCE (Need of dissolution)

1. Results from in-vitro dissolution rate experiments can be used to explain the observed differences in in-vivo availability.
2. Dissolution testing provides the means to evaluate critical parameters such as adequate bioavailability and provides information necessary to formulator in development of more efficacious and therapeutically optimal dosage forms.
3. Most sensitive and reliable predictors of in-vivo availability.
4. Dissolution analysis of pharmaceutical dosage forms has emerged as single most important test that will ensure quality of product.
5. It can ensure bioavailability of product between batches that meet dissolution criteria.
6. Ensure batch-to-batch quality equivalence both in-vitro and in-vivo, but also to screen formulations during product development to arrive at optimally effective products.
7. Physicochemical properties of model can be understood needed to mimic in-vivo environment.
8. Such models can be used to screen potential drug and their associated formulations for dissolution and absorption characteristics.
9. Serve as quality control procedures, once the form of drug and its formulation have been finalized.

An IR drug product is considered rapidly dissolving when a mean of 85 percent or more of the labeled amount of the drug substance dissolves within 30 minutes, using United States Pharmacopeia (USP) Apparatus 1 at 100 rpm or Apparatus 2 at 50 rpm (or at 75 rpm when appropriately justified in a volume of 500 mL or less (or 900 mL when appropriately justified) in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

An IR product is considered very rapidly dissolving when a mean of 85 percent or more of the labeled amount of the drug substance dissolves within 15 minutes, using the above mentioned conditions.

Question 14: What are Preformulation Studies and Area of Its Research?

Preformulation study is to develop the elegant (stable, effective, and safe) dosage form by establishing kinetic rate profile, compatibility with the other ingredients & establish Physico-Chemical parameter of new drug substance. Among these properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability are plays important role in Preformulation study. Polymorphism having crystal and amorphous forms shows different chemical physical and therapeutic description of the drug molecule.

MAJOR AREA OF PREFORMULATION RESEARCH

Bulk characterization:

1. Crystallinity & polymorphism,
2. Hygroscopicity,
3. Fine particle characterization,
4. Powder flow properties.

Solubility analysis:

1. Ionization constant –Pka
2. pH solubility profile,
3. Common ion effect-Ksp,
4. Solubilization,
5. Dissolution,
6. Partition co-efficient

Stability analysis:

1. Solution stability,
2. pH rate profile,
3. Solid state stability,
4. Bulk stability,
5. Stability in toxicology formulation.

Question 15: What is Biopharmaceutical Classification System (BCS)?

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: (1) dissolution, (2) solubility, and (3) intestinal permeability.5 According to the BCS, drug substances are classified as follows:

Class 1: High Solubility – High Permeability

Class 2: Low Solubility – High Permeability

Class 3: High Solubility – Low Permeability

Class 4: Low Solubility – Low Permeability

The recommended methods for determining solubility, permeability, and in vitro dissolution are discussed below.

A. Solubility

The solubility class boundary is based on the highest strength of an IR product that is the subject of a biowaiver request. A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media within the pH range of 1 - 6.8 at 37 ± 1°C. The volume estimate of 250 mL is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with an 8 fluid ounce glass of water.

B. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans, and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, other systems capable of predicting the extent of drug absorption in humans can be used (e.g., in situ animal, in vitro epithelial cell culture methods). A drug substance is considered to be highly permeable when the systemic BA or the extent of absorption in humans is determined to be 85 percent or more of an administered dose based on a mass balance determination (along with evidence showing stability of the drug in the GI tract) or in comparison to an intravenous reference dose.

C. Dissolution

An IR drug product is considered rapidly dissolving when a mean of 85 percent or more of the labeled amount of the drug substance dissolves within 30 minutes, using United States Pharmacopeia (USP) Apparatus 1 at 100 rpm or Apparatus 2 at 50 rpm (or at 75 rpm when appropriately justified in a volume of 500 mL or less (or 900 mL when appropriately justified) in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. An IR product is considered very rapidly dissolving when a mean of 85 percent or more of the labeled amount of the drug substance dissolves within 15 minutes, using the above mentioned conditions.

Question 16: What are Different types of dissolution apparatus?

DISSOLUTION APPARATUS AND DETAIL AS PER USP.		
APPARATUS	**NAME**	**DRUG PRODUCT**
Apparatus I	Rotating basket	Tablets
Apparatus II	Paddle	Tablets. capsules modified drug products
Apparatus III	Reciprocating cylinder	Extended-release drug products.
Apparatus IV	Flow cell	Drug products containing low-water-soluble drug

Question 17: What is Discriminatory dissolution media and how you develop it?

A. Discrimination, in the dissolution world, is having a dissolution test which will show a difference between one formulation and another. Basically, that you will be able to discriminate between a drug that passes and one that fails.

Discriminatory dissolution Media is which are sufficiently sensitive to highlight differences between innovator and test products.

Failure of dissolution can be due to a lot of factors (stability issues, poor formulation). A discriminatory test ideally should be able to show which samples are not working properly, so that they are not released to the public and may cause health concerns.

A discriminatory media is one part of a discriminatory dissolution test. The media should be able to meet sink condition (dissolve 3+ times the amount of drug), be a biologically relevant pH, contain as little surfactants or other solubilizers as needed. To determine a good media, typically it is best to study several different pH media, determine a couple which best dissolve your drug. If you haven't met sink, test the good media from your first experiment and try each with varying concentrations of surfactant until you get the lowest amount of surfactant needed to reach sink. You can verify the media by trying various formulations of the drug in the media if you wish, and see if it is able to discriminate the difference between multiple formulations (such as different coating levels, compression, etc.).

We can use the following modifications in the development of discriminatory dissolution testing:

1.	**Low rpm of the apparatus. (e.g. 25 rpm for paddle or 50 rpm for basket)**
2.	**Decreased volume of the dissolution media (500 ml)**
3.	**Modified pH (0.01 N in place of 0.1N HCL)**
4.	**Use of other Medias (e.g. dissolution in the mixture of IPA - water & use of Surfactants)**

Question 18: What are Modified Release Dosage Forms?

Most conventional (immediate release) oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration. In the formulation of conventional drug products, no deliberate effort is made to modify the drug release rate. Immediate-release products generally result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. In the case of conventional oral products containing prodrugs, the pharmacodynamic activity may be slow due to conversion to the active drug by hepatic or intestinal metabolism or by chemical hydrolysis. Alternatively, conventional oral products containing poorly soluble (lipophilic drugs), drug absorption may be gradual due to slow dissolution in or selective absorption across the GI tract, also resulting in a delayed onset time.

The pattern of drug release from modified-release (MR) dosage forms is deliberately changed from that of a conventional (immediate-release) dosage formulation to achieve a desired

therapeutic objective or better patient compliance. Types of MR drug products include delayed release (eg, enteric coated), extended release (ER), and orally disintegrating tablets (ODT).

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is a formulation in which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. Several types of modified-release oral drug products are recognized:

1. **Extended-release drug products.** A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.
2. **Delayed-release drug products.** A dosage form that releases a discrete portion or portions of drug at a time other than promptly after administration. An initial portion may be released promptly after administration. Enteric-coated dosage forms are common delayed-release products (eg, enteric-coated aspririn and other NSAID products).
3. **Targeted-release drug products.** A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.
4. **Orally disintegrating tablets (ODT).** ODT have been developed to disintegrate rapidly in the saliva after oral administration. ODT may be used without the addition of water. The drug is dispersed in saliva and swallowed with little or no water.

The term controlled-release drug product was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery. Other terms, such as ER, SR, XL, XR, and CD, are also used to indicate an extended-release drug product. Retarded release is an older term for a slow release drug product.

Question 19: Different types of granulation?

Wet granulation

In wet granulation, granules are formed by the addition of a granulation liquid onto a powder bed which is under the influence of an impeller (in a high-shear granulator), screws (in a twin screw granulator) or air (in a fluidized bed granulator). The agitation resulting in the system along with the wetting of the components within the formulation results in the aggregation of the primary powder particles to produce wet granules. The granulation liquid (fluid) contains a solvent or carrier material which must be volatile so that it can be removed by drying, and depending on the intended application, be non-toxic. Typical liquids include water, ethanol and isopropanol either alone or in combination. The liquid solution can be either aqueous based or solvent-based. Aqueous solutions have the advantage of being safer to deal with than other solvents.

Water mixed into the powders can form bonds between powder particles that are strong enough to lock them together. However, once the water dries, the powders may fall apart. Therefore, water may not be strong enough to create and hold a bond. In such instances, a liquid solution that includes a binder (pharmaceutical glue) is required. Povidone, which is a polyvinyl pyrrolidone (PVP), is one of the most commonly used pharmaceutical binders. PVP is dissolved in water or solvent and added to the process. When PVP and a solvent/water are mixed with powders, PVP forms a bond with the powders during the process, and the solvent/water evaporates (dries). Once the solvent/water has been dried and the powders have formed a more densely held mass, then the granulation is milled. This process results in the formation of granules.

The process can be very simple or very complex depending on the characteristics of the powders, the final objective of tablet making, and the equipment that is available. In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which are subsequently dried.

Wet granulation is traditionally a batch process in the pharmaceutical production; however, the batch type wet granulations are foreseen to be replaced more and more by continuous wet granulation in the pharmaceutical industry in the future. The shift from batch to continuous technologies has been recommended by the Food and Drug Administration. This continuous wet granulation technology can be carried out on a twin-screw extruder into which solid materials

and water can be fed at various parts. In the extruder the materials are mixed and granulated due to the intermesh of the screws, especially at the kneading elements.

Dry granulation

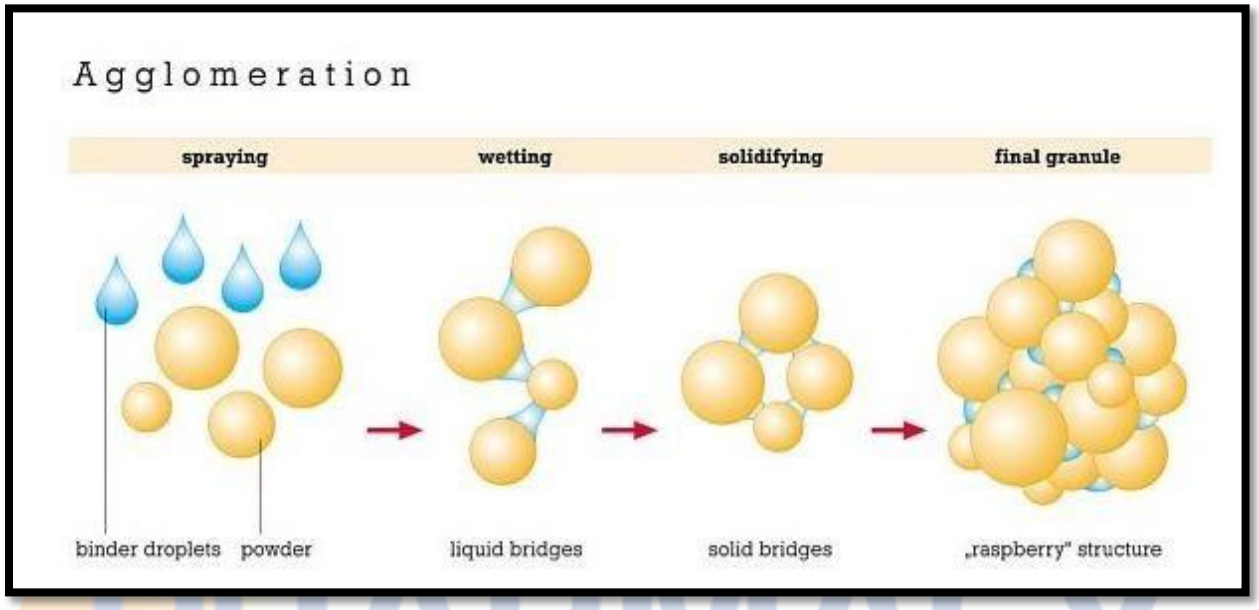
The dry granulation process is used to form granules without a liquid solution because the product granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. In this process the primary powder particles are aggregated under high pressure. A swaying granulator or a roll compactor can be used for the dry granulation.

Dry granulation can be conducted under two processes; either a large tablet (slug) is produced in a heavy duty tableting press or the powder is squeezed between two counter-rotating rollers to produce a continuous sheet or ribbon of material.

When a tablet press is used for dry granulation, the powders may not possess enough natural flow to feed the product uniformly into the die cavity, resulting in varying density. The roller compactor (granulator-compactor) uses an auger-feed system that will consistently deliver powder uniformly between two pressure rollers. The powders are compacted into a ribbon or small pellets between these rollers and milled through a low-shear mill. When the product is compacted properly, then it can be passed through a mill and final blend before tablet compression.

Typical roller compaction processes consist of the following steps: convey powdered material to the compaction area, normally with a screw feeder, compact powder between two counter-rotating rolls with applied forces, mill resulting compact to desired particle size distribution. Roller compacted particle are typically dense, with sharp-edged profiles.

Question 20: What are Different Stages of Wet Granulation?



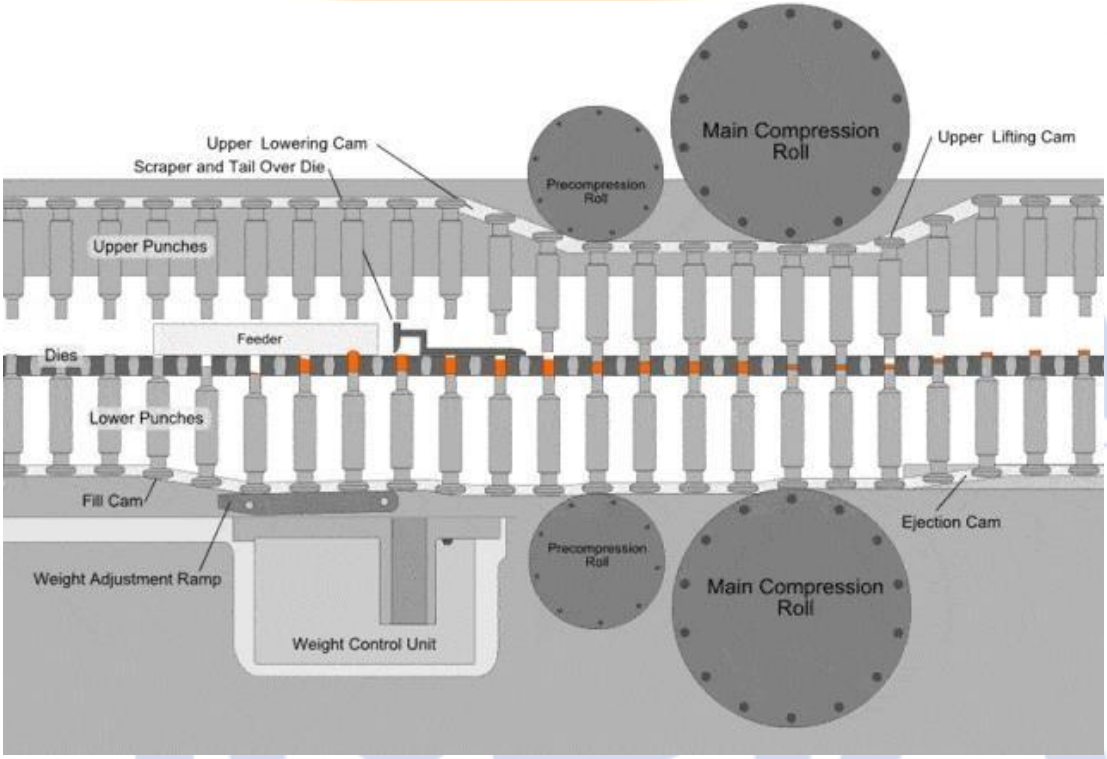
Question 21: What is Granulation End Point?

End-point can be defined by the formulator as a target particle size mean or distribution. Alternatively, the end-point can be defined in rheological terms. It has been shown that once you have reached the desired end-point, the granule properties and the subsequent tablet properties are very similar regardless of the granulation processing factors, such as impeller or chopper speed or binder addition rate. I would call this "the principle of equifinality". The ultimate goal of any measurement in a granulation process is to estimate viscosity and density of the granules, and, perhaps, to obtain an indication of the particle size mean and distribution. One of the ways to obtain this information is by measuring load on the main impeller. Mixer instrumentation, in general, has numerous benefits. In addition to a possible end-point determination, it can be used to troubleshoot the machine performance (for example, help detect worn-out gears and pulleys or identify mixing and binder irregularities). Instrumentation can serve as a tool for formulation fingerprinting, assure batch reproducibility, aid in raw material evaluation, process optimization and scale-up.

Question 22: Stages of Compression?

Principle of Tablet Compression Machine:

In the tablet compression machine main principle is compressing of the upper and lower punch in a die hole, the hydraulic pressure plays a key role. This pressure is transmitted unreduced through the static fluid. Any externally applied pressure is transmitted via static fluid to all the direction in same proportion. It also makes it possible to multiply the force as needed. If we increase the hydraulic pressure more compressing force on tablet then it becomes harder.



Different Stages of Tablet Compression Process:

Tablet compression process is divided into four distinct stage. These stage including filling, metering, compressing and ejection.

Tablet compressing stage

Filling	**Formulation is overfilled at the compressing station**
Metering	Overfill is removed
Compression	Tablet is formed by pressure of punches within die
Ejection	Tablet is ejected from die

1. **Filling:** The filling stage of tablet compression process involves transfer of raw materials into position for tablet compression. These raw materials have undergone prior processing by wet granulation, dry granulation (roller compaction), sizing or other process. The final formulation is then blended to yield a homogeneous blend. The blend then flows to the compressing machine punch-die cavity. The punch die cavity is composed of punch die and lower punch. The position of lower punch within the die determines the volume of the punch-die cavity. This volume must be appropriately sized for the weight of granulation to be compressed into tablets. The granulation is overfilled on the die table (turret) to ensure complete filling of the punch-die cavity volume.

2. **Metering:** The metering stage of the tablet compressing process involves removal of excess granulation from the compressing machine. This stage enables the exact weight (volume) of granulation to be compressed into tablets. The exact weight of granulation is controlled by the height of the lower punch in the die. The height of the lower punch is controlled by the metering cam (also called the dosage cam). The lower punch is raised to the appropriate level in the die to provide the exact weight of granulation in the punch-die cavity. The excess granulation is scraped from the surface of the die table. The metering stage is similar to the method used to measure flour when baking a cake. A measuring cup is first over-filled with flour; then a knife is used to scrape off the excess. The exact amount of flour is then left in the measuring cup.

3. **Compression:** The compression stage of the tablet compressing process forms the tablet. This stage involves bringing together the upper and lower punches under pressure within the die to form the tablet. As the punches enter the compressing stage, the upper and lower punches move between two large wheels called pressure rolls. These pressure rolls push the punches together to form the tablet. The distance between the upper and lower punches determines the thickness and the hardness of the tablet. When the punches are close together, a thin and hard tablet is created. When the punches are farther apart, the tablet made is softer and thicker. The proper balance of thickness and hardness determines the optimum roll distance for any specific product. These adjustments are made while keeping the tablet weight constant.

4. **Ejection:** The ejection stage of the tablet compressing process involves removal of the tablet from the lower punch-die station. In this stage, the upper punch retracts from the die cavity and rises above the turret table. Then the lower punch rises in the die, which in turn pushes the tablet upward to the top surface of the die table and out of the die cavity. A scraper (also called takeoff scraper or tablet rake-off) then pushes the tablet off the die table away from the compressing machine into the collection container.

Question 23: What are Tablet In Process Testing/QC Test?

Weight variation, Disintegration, Dissolution and Drug content. Non-Official Tests Hardness and Friability.

Official tests Weight variation test (uniformity of weight) •

Weigh 20 tablet selected at random, each one individually. X1, X2, X3… Xz

• Determine the average weight X= (X1+X2 +X3+…+ Xz)/20.

• Formula: Average Weight of Tablet – Individual Weight of Tablet / Average Weight of Tablet * 100. Limit Upper limit = average weight + (average weight *% error), Lower limit = average weight - (average weight * % error), The individual weights are compared with the upper and lower limits, NMT two of the tablets differ from the average weight of tablet.

Disintegration test (U.S.P.)

S.No	Type of tablets	Medium	Temperature	Limit
1	Compressed uncoated	-	37 ± 2^{0}C	15 minutes or as per individual monograph
2	Sugar coated If 1 or 2 tablets fail	Water 0.1 N HCL	37 ± 2^{0}C	60 minutes or as per individual monograph
3	Film coated	water	37 ± 2^{0}C	30 minutes or as per individual monograph
4	Enteric coated	0.1 N HCL and Phosphate buffer pH 6.8	37 ± 2^{0}C	1 hr or as per individual monograph
5	Dispersible/ Effervescent	water	37 ± 2^{0}C	LST < 3 minutes or as per individual monograph
6	Buccal	-	37 ± 2^{0}C	4 hr or as per individual monograph

Question 24: What are Core/Uncoated Tablets and Coated Tablets Defects and their remedies?

TABLET DEFECTS AND REMEDIES

- The defects related to Tableting Process

Capping: It is partial or complete separation of the top or bottom of tablet due air-entrapment in the granular material.

Reason: Capping is usually due to the air–entrapment in a compact during compression, and subsequent expansion of tablet on ejection of a tablet from a die.

Capping Related to Formulation

Causes

1. Large amount of fines in the granulation
2. Too dry or very low moisture content (leading to loss of proper binding action).
3. Not thoroughly dried granules.
4. Insufficient amount of binder or improper binder.
5. Insufficient or improper lubricant.
6. Granular mass too cold.

Remedies

1. Remove some or all fines through 100 to 200 mesh screen.
2. Moisten the granules suitably. Add hygroscopic substance e.g.: sorbitol, methyl-cellulose or PEG-4000.
3. Dry the granules properly.
4. Increasing the amount of binder.
5. Adding dry binder such as pre-gelatinized starch, gum acacia, powdered sorbitol, PVP, hydrophilic silica or powdered sugar.
6. Increase the amount of lubricant or change the type of lubricant.
7. Compress at room temperature.

Capping Related to Machine'(Dies, Punches and Tablet Press)

Causes

1. Poorly finished dies
2. Deep concave punches or beveled-edge faces of punches.
3. Lower punch remains below the face of die during ejection.

4. Incorrect adjustment of sweep-off blade.
5. High turret speed

Remedies

1. Polish dies properly. Investigate other steels or other materials.
2. Use flat punches.
3. Make proper setting of lower punch during ejection.
4. Adjust sweep-off blade correctly to facilitate proper ejection.
5. Reduce speed of turret (Increase dwell time).

Lamination: It is separation of tablet into two or more layers due to air-entrapment in the granular material.

Lamination Related To Formulation (Granulation)

Causes

1. Oily or waxy materials in granules.
2. Too much of hydrophobic lubricant. Eg. Magnesium-stearate.

Remedies

1. Modify mixing process. Add adsorbent or absorbent.
2. Use a less amount of lubricant or change the type of lubricant.

Lamination Related To Machine'(Dies, Punches and Tablet Press)

Causes

1. Rapid relaxation of the peripheral regions of a tablet, on ejection from a die.
2. Rapid decompression

Remedies

1. Use tapered dies, i.e. upper part of the die bore has an outward taper of 3° to 5°.
2. Use pre-compression step. Reduce turret speed and reduce the final compression pressure.

CRACKING Small, fine cracks observed on the upper and lower central surface of tablets, or very rarely on the sidewall are referred to as Cracks'.

Reason: It is observed as a result of rapid expansion of tablets, especially when deep concave punches are used.

Cracking Related To Formulation (Granulation)

Causes

1. Large size of granules.
2. Too dry granules.
3. Tablets expand.
4. Granulation too cold.

Remedies

1. Reduce granule size. Add fines.
2. Moisten the granules properly and add proper amount of binder.
3. Improve granulation. Add dry binders.
4. Compress at room temperature.

Cracking Related To Machine (Dies, Punches And Tablet Press)

Causes

1. Tablet expands on ejection due to air entrapment
2. Deep concavities cause cracking while removing tablets

Remedies

1. Use tapered die.
2. Use special take-off.

- **THE DEFECTS RELATED TO EXCIPIENT**

CHIPPING it is due to very dry granules. Chipping is defined as the breaking of tablet edges, while the tablet leaves the press or during subsequent handling and coating operations. Reason: Incorrect machine settings, specially mis-set ejection take-off.

Chipping Related To Formulation (Granulation)

Causes

1. Sticking on punch faces
2. Too dry granules.
3. Too much binding causes chipping at bottom.

Remedies

1. Dry the granules properly or increase lubrication.
2. Moisten the granules to plasticize. Add hygroscopic substances.

Chipping Related To Machine'(Dies, Punches And Tablet Press)

Causes

1. Groove of die worn at compression point.
2. Barreled die (center of the die wider than ends)
3. Edge of punch face turned inside/inward.
4. Concavity too deep to compress properly.

Remedies

1. Polish to open end, reverse or replace the die.
2. Polish the die to make it cylindrical
3. Polish the punch edges
4. Reduce concavity of punch faces. Use flat punches.

STICKING- Sticking' refers to the tablet material adhering to the die wall. Filming is a slow form of sticking and is largely due to excess moisture in the granulation.

Sticking Related To Formulation (Granulation)

Causes

1. Granules not dried properly.
2. Too little or improper lubrication.
3. Too much binder
4. Hygroscopic granular material.
5. Oily or way materials
6. Too soft or weak granules.

Remedies

1. Dry the granules properly. Make moisture analysis to determine limits.
2. Increase or change lubricant.
3. Reduce the amount of binder or use a different type of binder.
4. Modify granulation and compress under controlled humidity.
5. Modify mixing process. Add an absorbent.
6. Optimize the amount of binder and granulation technique.

Sticking Related To Machine (Dies, Punches And Tablet Press)

Causes

1. Concavity too deep for granulation.
2. Too little pressure.
3. Compressing too fast.

Remedies

1. Reduce concavity to optimum.
2. Increase pressure.
3. Reduce speed.

PICKING Picking'is the term used when a small amount of material from a tablet is sticking to and being removed off from the tablet-surface by a punch face. The problem is more prevalent on the upper punch faces than on the lower ones. The problem worsens, if tablets are repeatedly manufactured in this station of tooling because of the more and more material getting added to the already stuck material on the punch face. Reason: Picking is of particular concern when punch tips have engraving or embossing letters, as well as the granular material is improperly dried.

Picking Related To Formulation (Granulation)

Causes

1. Excessive moisture in granules.
2. Too little or improper lubrication.
3. Low melting point substances, may soften from the heat of compression and lead to picking.
4. Low melting point medicament in high concentration.
5. Too warm granules when compressing.
6. Too much amount of binder.

Remedies

1. Dry properly the granules, determine optimum limit.
2. Increase lubrication; use colloidal silica as a _polishing agent', so that material does not cling to punch faces.
3. Add high melting-point materials. Use high meting point lubricants.
4. Refrigerate granules and the entire tablet press.

5. Compress at room temperature. Cool sufficiently before compression.
6. Reduce the amount of binder, change the type or use dry binders.

Picking Related To Machine (Dies, Punches And Tablet Press)

Causes

1. Rough or scratched punch faces.
2. Bevels or dividing lines too deep.
3. Pressure applied is not enough; too soft tablets.

Remedies

1. Polish faces to high luster.
2. Design lettering as large as possible.
3. Plate the punch faces with chromium to produce a smooth and non-adherent face.
4. Reduce depths and sharpness.
5. Increase pressure to optimum.

BINDING :Binding‘ in the die, is the term used when the tablets adhere, seize or tear in the die. A film is formed in the die and ejection of tablet is hindered. With excessive binding, the tablet sides are cracked and it may crumble apart.

Binding Related To Formulation (Granulation)

Causes

1. Too moist granules and extrudes around lower punch.
2. Insufficient or improper lubricant.
3. Too coarse granules.
4. Too hard granules for the lubricant to be effective.
5. Granular material very abrasive and cutting into dies.
6. Granular material too warm.
7. sticks to the die.

Remedies

1. Dry the granules properly.
2. Increase the amount of lubricant or use a more effective lubricant.
3. Reduce granular size, add more fines, and increase the quantity of lubricant.
4. Modify granulation. Reduce granular size.
5. If coarse granules, reduce its size.

6. Use wear-resistant dies.
7. Reduce temperature.

Binding Related To Machine (Dies, Punches And Tablet Press)

Causes

1. Poorly finished dies.
2. Rough dies due to abrasion, corrosion.
3. Undersized dies. Too little clearance.
4. Too much pressure in the tablet press.

Remedies

1. Polish the dies properly.
2. Investigate other steels or other materials or modify granulation.
3. Rework to proper size. Increase clearance.
4. Reduce pressure. Or Modify granulation.

- **The defect related to more than one factor**

Mottling: It is either due to any one or more of these factors: Due to a colored drug, which has different color than the rest of the granular material (Excipient- related); improper mixing of granular material (Process-related); dirt in the granular material or on punch faces; oil spots by using oily lubricant.

- **The defect related to Machine**

Double Impression:

It is due to free rotation of the punches, which have some engraving on the punch faces. Double Impression involves only those punches, which have a monogram or other engraving on them. Reason: At the moment of compression, the tablet receives the imprint of the punch. Now, on some machines, the lower punch freely drops and travels uncontrolled for a short distance before riding up the ejection cam to push the tablet out of the die, now during this free travel, the punch rotates and at this point, the punch may make a new impression on the bottom of the tablet, resulting in _Double Impression‘.

Cause

1. Free rotation of either upper punch or lower punch during ejection of a tablet.

Remedies

1. Use keying in tooling, i.e. inset a key alongside of the punch, so that it fits the punch and prevents punch rotation.

MOTTLING Mottling‘ is the term used to describe an unequal distribution of colour on a tablet, with light or dark spots standing out in an otherwise uniform surface. Reason: One cause of mottling may be a coloured drug, whose colour differs from the colour of excipients used for granulation of a tablet.

Causes

1. A coloured drug used along with colourless or white-coloured excipients.
2. A dye migrates to the surface of granulation while drying.
3. Improperly mixed dye, especially during _Direct Compression‘.
4. Improper mixing of a coloured binder solution.

Remedies

1. Use appropriate colourants.
2. Change the solvent system, Change the binder, Reduce drying temperature and Use a smaller particle size.
3. Mix properly and reduce size if it is of a larger size to prevent segregation.
4. Incorporate dry colour additive during powder blending step, then add fine powdered adhesives such as acacia and tragacanth and mix well and finally add granulating liquid.

Tablet weight: Sources of variation The tablet weights are mainly affected by following reasons :

Product variation: This type of variation can be due to inconsistent powder density and particle size distribution. Density can change on the press, often because of overfilling of the die and re-circulation of the powder on the tablet press, whereas particle size distribution may change when the product becomes unblended during transfer or because of static electricity. This may also change because the product cannot withstand the handling and the mechanical stress it undergoes before reaching the tablet press.

Machine condition: The problems caused by a tablet press that is poorly prepared or operated are legion. The up and down motion under load on a new die table should be within 0.003 inch

of the setting. Care must be taken to ensure that the pressure rolls and cams are in very good condition.

Tooling condition: The punch working length should be taken in consideration. Working length is an important factor in how punches affect tablet weight. New tools are made to a tolerance of one-thousandth of an inch , the length of each punch is correct and identical.

Powder flow and feed-rates: Various defects are related to powder flow and feed-rates stem, therefore powder flow and feed-rates should be taken in account while manufacturing of tablets.

PROBLEMS AND REMEDIES FOR TABLET COATING

BLISTERING

It is local detachment of film from the substrate forming blister. Reason: Entrapment of gases in or underneath the film due to overheating either during spraying or at the end of the coating run.

Cause

1. Effect of temperature on the strength, elasticity and adhesion of the film.

Remedy

1. Use mild drying condition.

CRATERING

It is defect of film coating whereby volcanic-like craters appears exposing the tablet surface. The coating solution penetrates the surface of the tablet, often at the crown where the surface is more porous, causing localized disintegration of the core and disruption of the coating.

Causes

1. Inefficient drying.
2. Higher rate of application of coating solution.

Remedies

1. Use efficient and optimum drying conditions.
2. Increase viscosity of coating solution to decrease spray application rate.

PICKING

It is defect where isolated areas of film are pulled away from the surface when the tablet sticks together and then parts.

Reason: Conditions similar to cratering that produces an overly wet tablet bed where adjacent tablets can stick together and then break apart.

Cause

1. Inefficient drying.
2. Higher rate of application of coating solution.

Remedy

1. Use optimum and efficient drying conditions or increase the inlet air temperature.
2. Decrease the rater of application of coating solution by increasing viscosity of coating solution.

PITTING It is defect whereby pits occur in the surface of a tablet core without any visible disruption of the film coating. Reason: Temperature of the tablet core is greater than the melting point of the materials used in the tablet formulation.

Cause

1. Inappropriate drying (inlet air) temperature.

Remedy

1. Dispensing with preheating procedures at the initiation of coating and modifying the drying (inlet air) temperature such that the temperature of the tablet core is not greater than the melting point of the batch of additives used.

BLOOMING

It is defect where coating becomes dull immediately or after prolonged storage at high temperatures. Reason: It is due to collection on the surface of low molecular weight ingredients included in the coating formulation. In most circumstances the ingredient will be plasticizer.

Cause

1. High concentration and low molecular weight of plasticizer.

Remedy

1. Decrease plasticizer concentration and increase molecular weight of plasticizer.

BLUSHING

It is defect best described as whitish specks or haziness in the film. Reason: It is thought to be due to precipitated polymer exacerbated by the use of high coating temperature at or above the thermal gelation temperature of the polymers.

Causes

1. High coating temperature.

2. Use of sorbitol in formulation which causes largest fall in the thermal gelation temperature of the Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose, Methyl Cellulose and Cellulose ethers.

Remedies

1. Decrease the drying air temperature.
2. Avoid use of sorbitol with Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose, Methyl Cellulose and Cellulose ethers.

Colour variation

A defect which involves variation in color of the film. Reason: Alteration of the frequency and duration of appearance of tablets in the spray zone or the size/shape of the spray zone.

Cause

1. Improper mixing, uneven spray pattern, insufficient coating, migration of soluble dyes-plasticizers and other additives during drying.

Remedy

1. Go for geometric mixing, reformulation with different plasticizers and additives or use mild drying conditions.

INFILLING

It is defect that renders the intagliations indistinctness. Reason: Inability of foam, formed by air spraying of a polymer solution, to break. The foam droplets on the surface of the tablet breakdown readily due to attrition but the intagliations form a protected area allowing the foam to accumulate and settle. Once the foam has accumulated to a level approaching the outer contour of the tablet surface, normal attrition can occur allowing the structure to be covered with a continuous film.

Cause

1. Bubble or foam formation because of air spraying of a polymer solution.

Remedy

1. Add alcohol or use spray nozzle capable of finer atomization.

ORANGE PEEL/ROUGHNESS

It is surface defect resulting in the film being rough and nonglossy. Appearance is similar to that of an orange. Reason: Inadequate spreading of the coating solution before drying.

Causes

1. Rapid Drying
2. High solution viscosity

Remedies

1. Use mild drying conditions.
2. Use additional solvents to decrease viscosity of solution.

Cracking/Splitting

It is defect in which the film either cracks across the crown of the tablet (cracking) or splits around the edges of the tablet (Splitting). Reason: Internal stress in the film exceeds tensile strength of the film.

Cause

1. Use of higher molecular weight polymers or polymeric blends.
2. Use lower molecular weight polymers or polymeric blends. Also adjust plasticizer type and concentration.

BRIDGING

This occurs when the coating fills in the lettering or logo on the tablet and is typically caused by improper application of the solution, poor design of the tablet embossing, high coating viscosity, high percentage of solids in the solution, or improper atomization pressure. During drying, the film may shrink and pull away from the sharp corners of an intagliation or bisect, resulting in a ―bridging‖ of the surface. This defect can be so severe that the monogram or bisect is completely obscured. Remedy: Increasing the plasticizer content or changing the plasticizer can decrease the incidence of bridging.

Question 25: What are different types of tablet coating?

Different coatings

Tablets can either be **'sugar coated', 'film coated', 'enteric coated'** or coated to modify how the drug is released into the body **(modified release)**. Each of these coatings are there for different reasons and it is important to understand these reasons before deciding whether it is safe or appropriate to crush tablets.

This page **explains why** the coat may be on the tablet and what it means if you choose to crush or place the tablet in water to dissolve before swallowing.

Film and sugar coating

A **sugar coating** is basically is a **thick, hard coating of sugar** surrounding the tablet. It is no different in design to the sugar coatings placed on *Smarties® or Minstrels ®*. This is a traditional method used to hide the flavour of particularly unpleasant tasting drugs e.g. *ibuprofen and quinine*, both of which are very bitter. The other advantage of a sugar coating is that it can **prevent light or moisture from entering the tablet**, which causes the drug to break down too quickly.

Due to the **increase in tablet size** caused by sugar coating, drug manufacturers have largely changed to using **'film coatings'**. These are very thin layers of a safe ingredient placed around the tablet to again protect the tongue from the flavour of the contents and protect the contents from moisture and light. The film will break down with agitation and significant amounts of moisture (saliva or stomach acid) and therefore does not significantly affect the way in which the drug is absorbed into the body.

Crushing these tablets therefore may not seriously affect how the drug is released but may cause the resultant mixture to be unpleasant to taste.

Enteric coating

If a tablet is described as having an **'enteric coating' (e/c) or 'gastro-resistant'**, it means that there is a coating which is designed to hold the tablet together when in the stomach. This clever science relies on the fact that the **stomach is acid** and the intestines, where food goes after the stomach, are not. The coating is designed to hold together in acid conditions and **break down in non-acid conditions** and therefore release the drug in the intestines.

There are three reasons for putting such a coating on a tablet or capsule ingredient:

- To protect the stomach from the drug
- To protect the drug from the stomach
- To release the drug after the stomach e.g. in the intestines

The drugs which most commonly cause stomach ulcers like *aspirin, diclofenac and naproxen* are frequently available with enteric coatings. *Omeprazole*, which is a drug which stops the stomach from producing acid, is itself broken down in acid and therefore the drug generally has an enteric coating around it **either as a granule in the capsules or as a granule in the dispersible form**. *Sulfasalazine* is used either for the treatment of arthritis or for the treatment of Crohn's

disease which is inflammation of the intestines. When used for arthritis, it is very often given without an enteric coating so that it can be **absorbed more quickly**. For Crohn's, it is needed to work in the intestines so it is given an enteric coating.

It can be seen that an enteric coating has advantages and therefore such tablets or the contents of enteric coated capsules should never be crushed before being taken.

Modified release

'Modified release' means that the escape of the drug from the tablet has been modified in some way. Usually this is to **slow the release of the drug** so that the medicine does not have to be taken too often and therefore makes it easier to remember to take. The other benefit from modifying release is that the concentration of the drug in the body goes up slowly, is less likely to go very high and therefore **reduces the chance of side effects**.

Tablets and capsules which are designed to provide modified release often have the letters **MR, LA, XL, CR or SR** in their names e.g. *Diffundox MR, Elantan LA, Dilzem XL Calcicard CR, Dilcardia S.* Sometimes the words **'slow' or 'retard'** can be used to denote modified release e.g. *Diclomax retard, Voltarol retard & Slow K.*

There are a number of ways in which a medicine can have its release modified. Perhaps the most famous is that used in **Contac 400 capsules**. The pellets inside are of **different thicknesses** and therefore the thinnest release the drug first and the thickest last (Figure 1).

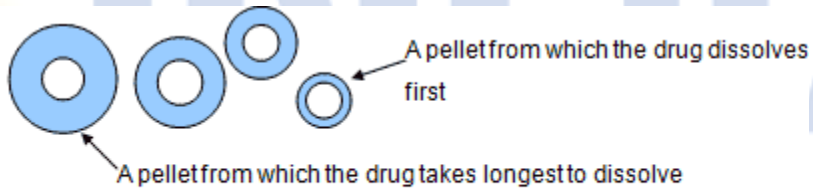


Figure 1: Drug pellets with coats of different thicknesses

Another method used is to put the drug in a viscous liquid which **breaks down slowly itself** and therefore releases the drug slowly. One method which has been tried in the past has been to put a **non-dissolving coating** around the tablet or capsule, laser a small hole in it and then **let the drug only release through the hole**. In such cases, patients frequently report passing the tablet or capsule whole and worrying whether it is actually working. Frequently, they are just **passing the outer coat in their stools** as this is how the medicine is designed to work and the drug has long been absorbed.

Modified release products usually have a higher than normal amount of the drug within them and therefore if they are crushed, the **whole dose** will be released very quickly and could be dangerous. Modified release products should never be crushed or modified before being taken.

Question 26: What do you mean by drug product specifications?

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval. Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which specifications are based, and adherence to Good Manufacturing Practices; e.g., suitable facilities, a validated manufacturing process, validated test procedure, raw material testing, in-process testing, stability testing, etc. Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.

Release vs. shelf-life acceptance criteria

The concept of different acceptance criteria for release vs. shelf-life specifications applies to drug products only; it pertains to the establishment of more restrictive criteria for the release of a drug product than are applied to the shelf-life. Examples where this may be applicable include assay and impurity (degradation product) levels. In Japan and the United States, this concept may only be applicable to in-house criteria, and not to the regulatory release criteria. Thus, in these regions, the regulatory acceptance criteria are the same from release throughout shelf-life; however, an applicant may choose to have tighter in-house limits at the time of release to provide increased assurance to the applicant that the product will remain within the regulatory acceptance criterion throughout its shelf-life. In the European Union there is a regulatory requirement for distinct specifications for release and for shelf-life where different.

In-process tests In-process tests,

Tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release. In-process tests which are only used for the purpose of adjusting process parameters within an operating range, e.g., hardness and friability of tablet cores which will be coated and individual tablet weights, are not included in the specification. Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or tighter than the release requirement, (e.g., pH of a solution) may be sufficient to satisfy specification requirements when the test is included in the specification. However, this approach should be validated to show that test results or product performance characteristics do not change from the in-process stage to finished product.

Question 27: What are the ICH Q guidelines?

[1] ICH Q1A (R2) - stability testing of new drug substances and products.

[2] ICHQ1B-stability testing: photo stability testing of new drug substances and products.

[3] ICH Q1C- stability testing for new dosage forms.

[4] ICH Q1D- bracketing and matrixing design for stability testing of new drug substances and products. [5] ICH Q1E- evaluation of stability data.

[6] ICH Q2 (R1)-validation of analytical procedures: text and methodology.

[7] ICHQ3A (R2)-impurities in new drug substances.

[8] ICHQ3B (R2)-impurities in new drug products.

[9] ICHQ3C (R5)-impurities: guidelines for residual solvents.

[10] ICHQ3D-guidelines for elemental impurities.

[11] ICHQ4B-pharmacopeias

[12] ICHQ5A (R1)-viral safety evaluation of biotechnology products derived from cell lines of human or animal origin.

[13] ICHQ5b- analysis of the expression construct in cells used for production of R-DNA derived protein products.

[14] ICHQ5C-stability testing of biotechnological/biological products.

[15] ICHQ5D- derivation and characterization of cell subtracts used for production of biotechnological/biological products.

[16] ICHQ5E-comparability of biotechnological/biological products subject to changes in their manufacturing process.

[17] ICHQ6A-specifications: test procedure and acceptance criteria for new drug substances and new drug products: chemical substances.

[18] ICHQ6B-specification: test procedures and acceptance criteria for biotechnological/biological products.

[19] ICHQ7-good manufacturing practice guide for active pharmaceutical ingredients.

[20] ICHQ8 (R2)-pharmaceutical development

[21] ICHQ9-quality risk management

[22] ICHQ10-pharmaceutical quality system

[23] ICHQ11-development and manufacture of drug substances (chemical entities and bio technological/biological entities.).

[24] ICHQ12-technical and regulatory considerations for pharmaceutical product life cycle management. [25] ICHQ13-continous manufacturing of drug substances and drug products.

[26] ICHQ14- analytical procedure development

Note: Refer each guidelines for detailed understanding

Question 28: What are the stability requirements for drug product submission?

For the general case, the recommended long-term and accelerated storage conditions for Climatic Zones III and IV are shown below

Study storage condition minimum time period covered by data at submission:

* Long-term 300C ± 20C / 65% RH ± 5% RH 12 Months.
* Accelerated 400C ± 20C / 75% RH ± 5% RH 6 Months.

No intermediate storage condition for stability studies is recommended for Climatic Zone III and IV. Therefore, the intermediate storage condition is not relevant, when the principle of test period or shelf life extrapolation described in Q1E are applied.

Aqueous based drug products packaged in semi-permeable containers:

Aqueous based drug products packaged in semi-permeable containers, the recommended long term and accelerated storage conditions for Climatic Zone III and IV are given below

* Long-term 300C ± 20C / 35% RH ± 5% RH 12 Months.
* Accelerated 400C ± 20C / not more than 25% RH ± 5% RH 6 Months.

Question 29: What do you mean by freeze thaw stability studies?

Freeze-thaw cycle testing is a part of stability testing that allows you to determine if your formula will remain stable under various conditions. This type of test puts your sample through a series of extreme, rapid temperature changes that it may encounter during normal shipping and handling processes. Freeze-thaw stability testing is highly recommended, especially for liquid-based cosmetics. These products may experience phase separation that can negatively affect the intended function.

Freeze-thaw testing is conducted by exposing the product to freezing temperatures (approximately -10 °C) for 24 hours, and then allowing it to thaw at room temperature for 24 hours. The sample is then placed in a higher temperature (approximately 45°C) for 24 hours and then placed at room temperature again for 24 hours. The sample is analyzed for significant changes. This completes one cycle. If, after three cycles of freeze-thaw testing, no significant changes are observed, you can be confident that the stability of your product is sufficient for transport.

It is generally conducted in liquid/semi-solid dosage forms.

Question 30: What do you mean by documentation/GDP?

Document is any written statement or proof of any activity in pharmaceuticals. Documentations are to define the manufacturers system of information & control, to minimize the risk of misinterpretation & errors inherent in oral or casually written communication, to provide unambiguous procedures to be followed to provide confirmation of performance, to allow calculations to be checked & to allow tracing of batch history. Documents are a mirror to show actual image of any pharmaceutical company. Documents and products are produced in pharmaceuticals but regulatory bodies are interested to see documents first. Different documents can describe the different activity in pharma and its actual image. Various documents are producing by pharma company would be discussed below. Due to the importance given to documentation in pharma “good documentation practices” is required. Good documentation is a systematic procedure of preparation, checking, verifying, issuing, storing and reviewing of any documents. Batch record is an important document kept along with reserve sample until one year of expiry of the product, and final products are release only after proper review of BMR, even after testing of Product from QC, product would not be released without review and completing

of BMR and other documents .every activity should be available written form as SOPs is a requirements of GMP. Control of document is also an important part of GDP to reduce error and misuses of any documents. Master copy for all activity should be prepared such as SOPs started from Draft copy and finalizes after checking and reviewing and Approved by QA documentation. Final copy should be printed as Master copy and stamped as "master copy" by red ink. A photocopy of master copy should be issued to concern department with stamped "control copy". A record should be maintained for issuing any documents with sign & date. Every document should have effective date, review date and revision no.

The GDP can be defined as "Good documentation practice is an essential part of the quality assurance and such, related to all aspects of GMP" this definition is based on WHO. Clearly written documents prevent errors of various activities in pharma each and every activity is written in specific documents such as SOPs and strictly followed. Spoken communications may be create errors so that all important documents such as Master formula record , procedure and record must be free from errors and Documented.
It is difficult to make a list of required documents and totally depend upon Companies activity or environment. Followings are the activity factors considered during designing of any documents.

1. Type of formulation
2. Country requirements
3. Availability of ERP or SAP system

Purpose of Documentations

• Defines specifications and procedures for all materials and methods of manufacture and control

• Ensures all personnel know what to do and when to do it

• Ensure that authorized persons have all information necessary for release of product

• Ensures documented evidence, traceability, provide records and audit trail for investigation

• Ensures availability of data for validation, review and statistical analysis.

Classification of Documentation

Following are the classification of Documents

• For organization & Personnel.

• For Buildings & facilities

• For Equipment.

• For Handling of R.M. & P.M.

• For Production & process control.

• For Packaging & Labeling control.

• For Holding & Distribution

• For Laboratory Control.

• For Records & Reports.

• For Return & Salvaged finished products.

Type of documents used in pharmaceuticals

• Specifications: as per MHRA Specifications describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation. We need specification for:

1. Active and inactive materials
2. Primary printed and packing materials
3. Intermediate and semi-finished product
4. Finished product

Question 31: What is SOP?

SOPs: it is a written, authorized functional instruction used as a reference by the person responsible for performance and are also used for training new operators in the performance of the procedure.

• Test method: it is a written and approved documents describe the detailed testing procedure.

• List: Documents contain a catalog of any object such as list of equipments.

• Certificates of Analysis: it is an authentic documents shows the analytical reports and decision of acceptance/rejections

• Label

• Records

• Organ gram

• Job description

Question 32: What is Batch Manufacturing Record (BMR)?

Batch Manufacturing records: it is an important document issued for every batch of product to assure, review and record keeping of any product batch. There are following major content of BMR.

1. Name of product, generic name, strength, shelf life, manufacturing date and expiry date.
2. A complete list of ingredients with full description, codes and quantity to be issued.
3. A statement for theoretical yield and reconciliation.
4. A complete MFG and control instructions, sampling and testing procedure, specification and precaution to be followed.
5. A statement for processing location and equipment.
6. The method or reference to method to be used for preparing the critical equipment including cleaning, assembling, calibrating and sterilizing.
7. Dates and time of all activities
8. Line clearance procedure in every steps
9. Labeling control and specimen for coding in primary, secondary and tertiary packing materials
10. Deviation record
11. Result of examine made.

Question 33: What do you mean by variations/Trend/OOS/OOT?

- **Variation:** means you won't usually have a perfect linear trend (analytical variability, sample uniformity)
- **Trends:** if the majority of stations show a trend (downward, upward), consider it a trend.
- **Out of Trend (OOT):** analytical value outside our experience but within the specification (no OOS)
- **OOS (Out of Specification)**: analytical value outside of the registered specification

Question 34: What do you mean by "Significant Change" during stability testing?

For an API: "significant change" is failure to meet the specification for any parameter

For a Finished Pharmaceutical Product (FPP), significant change is any of:

- Any degradation product exceeding its limit
- Failure in tests of appearance, physical attributes and functionality test, e.g. colour, hardness, pH
- > 5% change in assay from initial, i.e. t0 (Initial time point)
- failure to pass dissolution testing for 12 dosage units (fail S2)

Question 35: What do you mean by CAPA?

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining root cause. The level of effort and formality of the investigation should be commensurate with the level of risk. CAPA methodology should result in product and process improvements and enhanced product and process understanding. CAPA is a concept within good manufacturing practice (GMP). It focuses on the systematic investigation of the root causes of non-conformities in an attempt to prevent their recurrence (for corrective action) or to prevent occurrence (for preventive action).

Implementation of Corrective & preventive actions is the path towards improvement & effectiveness of Quality Management system. Corrective actions are nothing but the action/s based on the problem identification. The problem or a non-conformance can be identified internally through staff suggestions, management reviews, document reviews or internal audits. Customer complaints / suggestions, customer rejections, non-conformities raised in customer / third party audits & recommendations by the auditors are the external sources which lead to find the root cause of the problem.

Corrective action is a reaction to any of the cause/non-conformance mentioned above & can be divided in two phases of action:

1) Identification of root cause: for this purpose TQM tools such as fish-bone or cause & effects analysis can be practiced. Your CAPA would be appropriate & effective if & only if you have identified the root cause of problem.

2) Taking necessary actions: in order to address the root cause takes necessary immediate action/s. The effectiveness of the corrective action taken has to be verified periodically through a systematic approach of PDCA (Plan - Do - Check - Act) cycle.

Preventive action is prediction of problem & trying to avoid the occurrence (fail safe) through self-initiated action/s & analysis related with your processes / products. This can be initiated with the help of active participation of staff members / workers through improvement teams, improvement meetings, management review, customer feedback & deciding own goals quantized in terms of business growth, reducing rejections, utilizing the equipment effectively etc.

Question 36: What do you mean by QbD?

The pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance.

QbD development process includes:

- Begin with a target product profile that describes the use, safety and efficacy of the product
- Define a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development
- Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use risk assessment to prioritize knowledge gaps for further investigation
- Design a formulation and identify the critical material (quality) attributes of the final product that must be controlled to meet the target product quality profile.
- Design a manufacturing process to produce a final product having these critical materials attributes.

- Identify the critical process parameters and input (raw) material attributes that must be controlled to achieve these critical material attributes of the final product. Use risk assessment to prioritize process parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a design space or other representation of process understanding.
- Establish a control strategy for the entire process that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment.
- Continually monitor and update the process to assure consistent quality.

Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools that may be used in the QbD process when appropriate. They are not check-box requirements.

Traditional approach & Enhanced QbD approach

Aspects	Current	QbD
Pharmaceutical Development	Empirical, Random, Focus on optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, managed by company's quality systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release possible

Advantages of QbD

Benefits for Industry:

- Better understanding of the process.
- Less batch failure.
- More efficient and effective control of change.
- Return on investment / cost savings.

Additional opportunities:

- An enhance QbD approach to pharmaceutical development provides opportunities for more flexible regulatory approaches.

Ex: Manufacturing changes within the approved design space without further regulatory review.

- Reduction of post-approval submissions.
- Better innovation due to the ability to improve processes without resubmission to the FDA when remaining in the Design Space.
- More efficient technology transfer to manufacturing.
- Greater regulator confidence of robust products.
- Risk-based approach and identification.
- Innovative process validation approaches.
- Less intense regulatory oversight and less post-approval submissions.
- For the consumer, greater drug consistency.
- More drug availability and less recall.
- Improved yields, lower cost, less investigations, reduced testing, etc.
- Time to market reductions: from 12 to 6 years realized by amongst others.
- First time right: lean assets management.
- Continuous improvement over the total product life cycle (i.e. controlled, patient guided variability).
- Absence of design freeze (no variation issues).
- Less validation burden.
- Real time controls (less batch controls).
- Realistic risk perceptions.
- Contributes substantially to realize the better, cheaper and safer mandate.

Question 37: What do you understand by QTPP (Quality Target Product Profile?

The quality target product profile (QTPP) as defined in ICH Q8(R1) is a summary of the quality characteristics or attributes of a drug product that ideally will be achieved and thereby ensure the safety and efficacy of a drug product. The QTPP forms the basis of design for the development of the product and is developed with the end in mind. It is both prospective, that is, it describes the goals for the development team, and dynamic, that is, the QTPP may be updated or revised at various stages of development as new information is obtained during the development process. The FDA has published a guidance defining the Target Product Profile (TPP), that focuses on the consumer (patient) and the desired product label. The QTPP is a subset of the TPP and is more oriented towards the chemistry, manufacturing and controls (CMC) aspects of development.

Question 38: What do you understand by CQAs (Critical Quality Attrubutes)?

A critical quality attribute as defined by ICH Q8(R2) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with raw materials (drug substance, Excipients), intermediates (in-process materials), and drug product. Drug product CQAs derived from the QTPP are used to guide the product and process development. Drug product CQAs are the properties that are important for product performance, that is, the desired quality, safety, and efficacy. Depending on the CR dosage form, these may include the aspects affecting the purity, potency, stability, drug release, microbiological quality, and so on. CQAs can also include those properties of a raw material that may affect drug product performance or manufacturability. An example of this would be drug substance particle size distribution (PSD) or bulk density that may influence the flow of a granulation and therefore the manufacturability of the drug product. Similarly, the dissolution from a controlled release dosage form is dependent on the particle size of the polymer and the hardness of tablet. In this example, PSD and hardness can be designated as CQA's. They are also commonly referred to as critical material attributes (CMA).

Question 39: What do you understand by BE studies?

Bioequivalence is a term in pharmacokinetics used to assess the expected in vivo biological equivalence of two proprietary preparations of a drug. If two products are said to be bioequivalent it means that they would be expected to be, for all intents and purposes, the same. Birkett (2003) defined bioequivalence by stating that, "two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards.

For The World Health Organization (WHO) "two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate (Cmax and tmax) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same" .

The United States Food and Drug Administration (FDA) has defined bioequivalence as, "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."

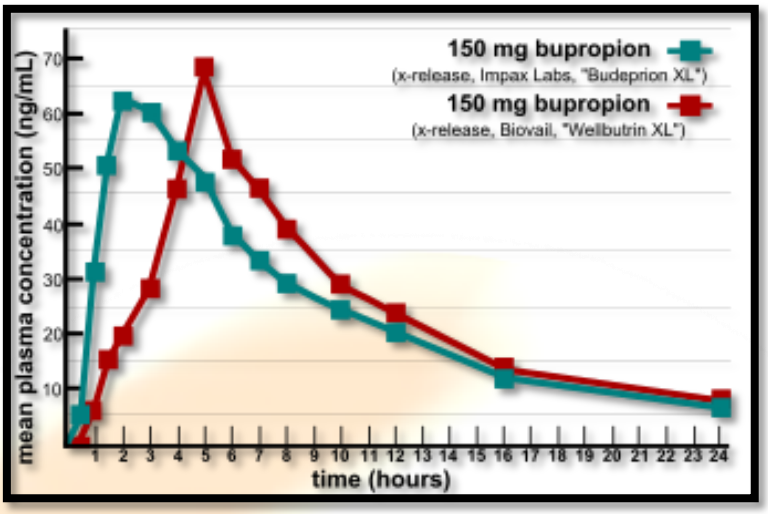


Figure: A bioequivalency profile comparison of 150 mg extended-release bupropion as produced by Impax Laboratories for Teva and Biovail for GlaxoSmithKline.

In determining bioequivalence, for example, between two products such as a commercially available Brand product and a potential to-be-marketed Generic product, pharmacokinetic studies are conducted whereby each of the preparations are administered in a cross-over study to volunteer subjects, generally healthy individuals but occasionally in patients. Serum/plasma samples are obtained at regular intervals and assayed for parent drug (or occasionally metabolite) concentration. Occasionally, blood concentration levels are neither feasible nor possible to compare the two products (e.g. inhaled corticosteroids), then pharmacodynamic endpoints rather than pharmacokinetic endpoints (see below) are used for comparison. For a pharmacokinetic comparison, the plasma concentration data are used to assess key pharmacokinetic parameters such as area under the curve (AUC), peak concentration (C_{max}), time to peak concentration (T_{max}), and absorption lag time (t_{lag}). Testing should be conducted at several different doses, especially when the drug displays non-linear pharmacokinetics.

In addition to data from bioequivalence studies, other data may need to be submitted to meet regulatory requirements for bioequivalence. Such evidence may include:

- analytical method validation
- *in vitro-in vivo* correlation studies (IVIVC)

Regulatory Requirements:

The World Health Organization

The World Health Organization considers two formulation bioequivalent if the 90% confidence interval for the ratio multisource (generic) product/comparator lie within 80.00-125.00% acceptance range for AUC_{0-t} and C_{max}. For high variable finished pharmaceutical products, the applicable acceptance range for C_{max} can be 69.84-143.19%.

Australia

In Australia, the Therapeutics Goods Administration (TGA) considers preparations to be bioequivalent if the 90% confidence intervals (90% CI) of the rate ratios, between the two preparations, of C_{max} and AUC lie in the range 0.80–1.25. T_{max} should also be similar between the products.

There are tighter requirements for drugs with a narrow therapeutic index and/or saturable metabolism – thus no generic products exist on the Australian market for digoxin or phenytoin for instance.

Europe

According to regulations applicable in the European Economic Area two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same. This is considered demonstrated if the 90% confidence intervals (90% CI) of the ratios for AUC_{0-t} and C_{max} between the two preparations lie in the range 80–125%.

United States

The FDA considers two products bioequivalent if the 90% CI of the relative mean C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of the test (e.g. generic formulation) to reference (e.g. innovator brand formulation) should be within 80% to 125% in the fasting state. Although there are a few exceptions, generally a bioequivalent comparison of Test to Reference formulations also requires administration after an appropriate meal at a specified time before taking the drug, a so-called "fed" or "food-effect" study. A food-effect study requires the same statistical evaluation as the fasting study, described above.

Question 40: What are the critical Process Parameters for Tablet Manufacturing?

Unit operation	Process parameter	Quality attributes
Mixing	1. Order of addition 2. Mixer load level 3. Impeller speed and time 4. Chopper speed and time 5. Chopper ON/OFF Pattern 6. Mixing time	Particle size distribution Bulk/tapped density Moisture content Flow properties
Milling	1. Impact/cutting/screening mills direction. 2. Speed of mill 3. Screen size 4. Feeding rate	Particle size Particle shape Flow properties Polymorphic form
Wet Granulation (RMG)	1. Pre-binder addition mix time 2. Impeller speed and ON time 3. Chopper speed and ON time 4. Binder fluid temperature 5. Binder addition rate and time 6. Post-granulation mix time	Blend uniformity Flow, Moisture content Particle size and distribution addition Granule size and distribution Granule strength and uniformity Solid form
Spray Granulation (FBE)	1. Spray nozzle type and location 2. Binder addition rate and time 3. Bowel temperature 4. Fluid bed granulations Mixing time Spray nozzle (type/quantity/ pattern/configuration) 5. Binder fluid temperature 6. Inlet air flow rate, volume, temperature, and dew point 7. Exhaust air temperature, 8. Shaking intervals	Blend uniformity Flow Moisture content Particle size and distribution addition Granule size and distribution Granule strength and uniformity Solid form Moisture content, Residual solvents

	9. Product temperature	
Drying (FBD)	1. Inlet air flow rate, volume, temperature, and dew point 2. Bowel temperature 3. Exhaust air temperature, 4. Shaking intervals 5. Product temperature	Granule size and distribution Granule strength, and uniformity Particle size Flow Bulk/tapped density, Moisture content Residual solvents
Drying (Tray dryer)	1. Tray Quantity carts and trays per chamber 2. Quantity of product per tray 3. Drying time and temperature 4. Air flow 5. Inlet air temperature and dew point 6. Jacket temperature 7. Condenser temperature 8. Vacuum strength	Granule size and distribution Granule strength, and uniformity Particle size Flow Bulk/tapped density, Moisture content Residual solvents.
Roller compaction	1. Roll speed 2. Gap setting 3. Roll pressure 4. Auger screw rate 5. Roller type	Appearance Ribbon/particle size and shape Ribbon density, strength, and thickness Solid form
Blending	1. Blender type 2. Blender RPM 3. Blending time	Blend uniformity Flow properties
Compression	1. Compression speed 2. Force Pre-compression 3. Force main compression 4. Force Feed frame type and speed 5. Hopper design, height, 6. Depth of fill 7. Punch penetration depth	Target weight, Weight uniformity Content uniformity, Hardness Thickness, Tablet porosity Friability

Coating	1. Product temperature 2. Total pre-heating time 3. Spray nozzle (type/quantity/ pattern/configuration) 4. Individual gun spray rate 5. Total spray rate 6. Pan rotation speed 7. Atomization air pressure Pattern 8. Air pressure 9. Inlet air flow, temperature, dew point 10. Exhaust air temperature, air flow 11. Product temperature 12. Total coating time	Visual attributes, Moisture content, Weight of core tablets Appearance, Visual attributes , % Weight gain, Film thickness, Color uniformity , Hardness Thickness

Question 41: How to select blend uniformity samples and what are the acceptance criteria?

1. Carefully identify at least 10 sampling locations in the blender to represent potential areas of poor blending. For example, in tumbling blenders (such as V-blenders, double cones, or drum mixers), samples should be selected from at least two depths along the axis of the blender. For convective blenders (such as a ribbon blender), a special effort should be made to implement uniform volumetric sampling to include the corners and discharge area (at least 20 locations are recommended to adequately validate convective blenders).

2. Collect at least 3 replicate samples from each location.

Samples should meet the following criteria:

• Assay one sample per location (number of samples (n) ≥ 10) (n = 20 for ribbon blender).

• RSD (relative standard deviation) of all individual results ≤ 5.0 percent.

• All individual results are within 10.0 percent (absolute) of the mean of the results.

Details: http://academy.gmp-compliance.org/guidemgr/files/5831DFT.PDF

Question 42: What do you understand by Uniformity of Dosage Units?

To ensure the consistency of dosage units, each unit in a Suspension, batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit. The uniformity of dosage units specification is not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for external, cutaneous administration. The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. The uniformity of dosage units can be demonstrated by either of two methods, Content Uniformity or Weight Variation.

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			≥25 mg and ≥25%	<25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Solutions in unit-dose containers and into soft capsules			WV	WV
Others			CU	CU

Note/Disclaimer: For more details we would recommend to explore the regulatory guidelines, reputed books and review/research article. These answers only provide basic understanding. These answers will assist you but does not guarantee for cracking the interview.

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