Chapter 6

Introduction
To
Experimental......
DOSE CONSIDERATION\textsuperscript{1-6}

Duration of most illness is longer than therapeutic effect produced by a single dose. An optimal multiple dosage regimen is the one in which the drug is administered in suitable dosages, with sufficient frequency that ensured maintenance of plasma concentration within the therapeutic window.

The degree of fluctuation between the highest and lowest plasma concentrations $C_{\text{max}}$ and $C_{\text{min}}$ is proportional to dose size. Similarly if the dosing frequency is reduced, the plasma concentrations produced are lower and the ratio $C_{\text{max}}/C_{\text{min}}$ are higher. Higher dose and frequency, results in greater accumulation and toxicity. Generally, dosing frequency similar to plasma half-life of the drug ($T=\tau_{\text{h}}$) leads to better therapeutic success.

Generally five half lives or doses are required to achieve reasonably constant plasma concentrations. To avoid this delay, priming or loading does is administered followed by regular doses or maintenance doses. The loading dose, which may be up to about twice the maintenance dose, pushes the plasma concentration to desired level, which is then maintained by the maintenance doses.

In case of controlled/extended release orally dosage forms, assuming that (i) drug disposition follows first-order kinetics, (ii) the rate-limiting step in the absorption is rate of drug release from the formulation, and (iii) the released drug is rapidly and completely absorbed, four general models for drug input based on the drug release pattern can be defined: (i) zero-order release, (ii) first-order release, (iii) initial rapid first order release of loading dose followed by zero-order release, and (vi) initial rapid first order release of loading dose followed by first-order release.
the drug released from ER formulations is stable zero-order in fluids at the absorption site and has similar absorption efficiency from all encountered absorption sites, its rate of appearance in plasma will be governed by its rate of release. Thus, in this case chances of obtaining flatter plasma concentration will be better. First order release systems, although easier to design, have limitation compared to zero-order systems. This is because with first order release characteristic, release rate falls with time as the formulation advances along intestinal tract; the absorption efficiency generally decreases due to reason likes (i) reducing surface area, (ii) increasing viscosity, and (iii) decreasing mixing. In case of last two models i.e., "initial rapid first order release", an initial dose is rapidly release (immediate release fraction) for immediate first-order availability, while the remaining amount is released (sustained release fraction) at a slow zero or first order. Both the fractions are built in the same unit of the dosage form e.g., tablets. Such a formulation is ideally suited for drugs with long $t_{1/2}$ in which case attainment of plateau would have otherwise taken a long time. The slow release component should ideally begin releasing the drug when the drug level from the faster release component is at the peak. Repeated administration of such type of dosages may result into increased fluctuations in the plasma concentration. To minimize this, one could plan for

(i) Decreasing the loading dose in the subsequent dosage forms,

(ii) Increasing the dosing interval, or

(iii) Incorporating sufficiently small portion of the drug in the immediate release fraction.

Usually the last mentioned option is most suitable.

Various pharmacokinetic models$^7\sim^{12} $ are proposed for calculating dose and release profile of ER dosage form. According to model proposed by Rowland and Beckett,

Total dose ($W$) in ER formulation is given by

$$ W = (W_0 + 0.693 W_0 \cdot f \cdot h) / t_{1/2} $$

(6.1.)
where  
\[ W_0 = \text{dose giving clinical response in conventional dose} \]
\[ f = \text{absorption factor} \]
\[ t_{1/2} = \text{half life} \]
\[ h = \text{number of hours.} \]

According to model proposed by Dobrinska and Welling,

Total dose \((W)\) in ER formulation is given by

\[ W = (C_{ss} \cdot V_d \cdot K_{el} \cdot T) + (C_{ss} \cdot V_d \cdot K_{el}) / K_{el} \]  \hspace{1cm} (6.2)

where \(C_{ss} = \text{steady state plasma concentration}\)
\(V_d = \text{volume of distribution}\)
\(K_{el} = \text{elimination constant}\)
\(T = \text{number of hours.}\)

In this work zero order and first order release models based on the above models is attempted.

6.2. ORAL EXTENDED RELEASE SYSTEM

Over past two decades, ER Dosage Form particularly, multi-particulate oral drug delivery (DD) and oral matrix DD have become extremely popular for controlling the release of drug from solid dosage form. They are the focus of pharmaceutical dosage form technology and are been continuously developed in order to enhance clinical efficiency and reduce total disease management cost, thereby providing economic merit to the society. The term “ER dosage form” can be used for dosage forms to indicate that the drug release kinetics is predictable and reproducible from one unit to another, whether or not the kinetics followed is zero order.

6.2.1. Continuous Extended Release System

These systems release the drug for a prolonged period of time along the entire length of \textit{g.i.t.} especially up to the terminal region of small intestine, with normal transit of the dosage form. These systems are:
Dissolution controlled release systems
(v) Slow dissolving salts and complexes
Diffusion controlled release systems
(vi) pH-dependent formulations
Dissolution and diffusion controlled release systems
(vii) Osmotic pressure controlled systems
Ion-exchange resin-drug complexes
(viii) Hydrodynamic pressure controlled systems

6.2.2. Delayed Transit And Continuous Release System

These systems are designed to prolong their residence in the g.i.t. along with their release. Often, the dosage form is fabricated to retain in the stomach and hence the drug present therein should be stable to gastric pH. Systems are:

- Altered density systems
- Size-based systems
- Mucoadhesive systems

6.2.3. Delayed Release System

These systems include drugs, which are unstable under certain conditions of g.i.t., may cause g.i.t. distress, absorbed from a specific g.i.t. site or meant to exert local effects at a specific g.i. site. Systems are

- Intestinal release systems
- Colonic release systems

In this work, the first variety i.e., continuous release systems incorporating diffusional mechanisms and/or dissolution is attempted.

6.3. PREFORMULATION STUDIES

“It is a capital mistake to theorize before one has data”,

Scandal in Bohemia, Sir Arthur Conan Doyle.13
Preparation can be defined as a reconnaissance in depth to define the properties of a drug molecule likely to affect the design and performance of the drug delivery system (DDS). Although preformulation data do not necessarily tell us which path to follow in formulation work, it very often does inform us which path are dead ends. Originally, preformulation was largely concerned with how possible incompatibilities between drugs and excipients might affect the stability of drug formulation. However, when, during the 1960's an increasing body of experimental data clearly demonstrated the deficiencies in vivo of then commercialized drug products, the biopharmaceutical aspects of preformulation became increasingly important.

Preformulation is the study of the chemical and physical properties of the drug compounds prior to the developmental process of the formulation. The purpose of the study is to understand the nature and characteristic of each component and to optimize conditions of the dosage form manufacture. Before development, preformulation data must be generated to aid development process and physicochemical properties must be defined. The interaction (excipient compatibility) between the drug and the excipients to be used in the formulation are included in the study for intelligent selection of excipients. Drug degradation profiles are also to be included in the study. Analytical characteristics are included for development of technique, so as to monitor process during formulation development stage. Stages of preformulation include:

- Preformulation report on physicochemical properties and analytical testing of drug.
- Preformulation report on data for development of dosage form.
- Preformulation report on data to support for Quality and Finished product Manufacturing.
1. Preformulation Reports

Preformulation studies report include:

- **Analytical Profiles** as is required for analytical method development, which include identification technique of drug, purity studies that include degradation and residual solvent analysis, and chemical properties of drug.

- **Physiochemical Properties** such as partition coefficient, dissociation constant, pKa, solubility. pKa can be estimated using Henderson-Hasselbalch equation from UV spectrophotometry, titration or solubility studies. Solubility studies are essential from understanding bioavailability (absorption of drug) and setting up *in vitro* dissolution techniques. Solubility studies are carried in solution (pH 1.0 to 7.5) and in solvents.

- **Pharmaceutical and Mechanical Properties**, which will include hygroscopicity and moisture absorption/desorption, powder characteristics – density, flow and compression property.

- **Solid-state Characteristics** such as solid state, particle size, surface area, biopharmaceutical properties, polymorphism, hydrates and solvates.

- **Excipient Compatibility** for selection of excipient. This study focuses on binary mixture of drug substances and selected excipient in fixed ratio with or without water. The mixture is stored at elevated temperature in capped vials. The results of interaction may be determined by visual observation, TLC, HPLC, UV and DSC.
However, the importance attached to stability aspects of preformulation has in many companies tended to decrease\textsuperscript{14}. Monkhouse\textsuperscript{16-17} has argued articulately and powerfully that some types of preformulation tests for incompatibilities are academic in the worst sense of word. He has indicated that studies in which powder mixtures of say 50% drug and 50% excipient exposed to storage at elevated temperature may well show interactions, but whether or not such interactions are of practical importance may well be debatable. In the finished dosage form, the excipient may only be present at the 1% level and drug at 1%. Under such conditions, the formulation, may well prevent the incompatibility from ever having any practical effect. As a result of these criticisms and, in some cases, after examination of their own experimental data, certain companies in the pharmaceutical industry have recently reduced the scope of their incompatibility testing. However, stability studies of the pure drug substance remain an essential part of preformulation studies. Besides, this, it forms a regulatory requirements for NDA's by FDA and other regulatory agencies.

The different techniques employed for the evaluation during the preformulation studies are:

6.4. SPECTRAL METHODS USED FOR CHARACTERIZATION DURING PREFORMULATION

The most often-employed spectral study methods include (a) absorption spectroscopy; (b) infra red spectroscopy; and (c) X-ray diffraction spectroscopy.

All atoms and molecules are capable of absorbing energy in accordance with certain restrictions; these limitations depend upon the structure of the substance. The kind and amount if radiation absorbed by a molecule depend on the structure of molecule,
The amount of radiation absorbed also depends upon the number of molecules interacting with the radiation.

### 6.4.1. Absorption Spectroscopy

Absorption spectroscopy is one of the most valuable analytical techniques invented. Its advantages include speed, simplicity, specificity and sensitivity.

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### 6.4.2. Ultra-Violet Visible Spectroscopy\(^{18-20}\)

**Principle:** When radiation is passed through a layer of a solution containing an absorbing substance, part of the radiation is absorbed; the intensity of the radiation emerging from the solution is less than the intensity of the radiation entering it. The magnitude of the absorption is expressed in terms of the absorbance, \(A\), defined by the expression

\[
A = \log_{10} \left( \frac{l_0}{l} \right) \quad (6.3)
\]

where
\[
I_0 = \text{intensity of the radiation passing into the absorbing layer}
\]
\[
l = \text{intensity of the radiation passing out of it.}
\]

The absorbance depends on the concentration of the absorbing species in the solution and the thickness of the absorbing layer for measurement.

The absorption spectra of a compound can be measured in very dilute solution against a solvent blank using an automatic recording spectrophotometer. For
colorless compounds, measurements are made in the range of 200-400 nm, for colored compounds, the range is 400-700 nm.

UV-visible spectroscopy can be used to determine many physicochemical characteristics of compounds and thus can provide information as to the identity of a particular compound.

Although UV-visible spectra do not enable absolute identification of an unknown, they are frequently used to confirm the identity of a substance through comparison of the measured spectrum with a reference spectrum. Where spectra are highly similar, derivative spectroscopy may be used. Derivative spectra can be useful in qualitative analysis, either for characterizing materials or for identification purposes. Derivative spectra can be used to enhance difference among spectra, to resolve overlapping bands in qualitative analysis and, most importantly, to reduce the effects of interferences from scattering, matrix, or other absorbing compounds in quantitative analysis.

6.4.3. Calibration of UV-Visible Spectrophotometer

Various parameters to be calibrated for UV-Visible spectrophotometer include (i) accuracy; (ii) wavelength accuracy; (iii) stray light (220 nm and 340 nm); (iv) drift; and (v) noise. Most commonly recommended method for checking absorbance accuracy is to use solution of potassium dichromate (6.006 mg/100mL in 0.005 N H₂SO₄). It exhibits characteristic spectral graph having minima (valley) at 235 nm, 313 nm; and maxima at 257 nm and 350 nm.

Filters having calibration traceable to international standards can also be used for checking the various parameters. Usually, a set of four neutral density filters is
available. Holmium filter for absorbance accuracy, Didymium filter for wavelength accuracy and two filters designed to assess stray light at 220 nm and 340 nm. Also 1.2% solution of KCl can be used to check the level of stray light. For calibration of wavelength, tolerance of ± 1 nm in the range of 200-400 nm and ± 3 nm in visible range is usually recommended.

6.4.4. Infra Red Spectroscopy\textsuperscript{18-20}

Infrared radiation refers broadly to that part of the electromagnetic spectrum between the visible and microwave region. It can be divided into the near infrared region (0.7 –2.5 µm) and the far infrared region (14.3 – 50 µm).

The frequencies of the normal vibrations of molecules, i.e., the position of the spectrum bands obtained (expressed in wavelengths or in wave numbers) are determined by the masses of the atoms of the molecules and the forces acting between the masses. Consequently infrared spectra are individual to a high degree.

Although the infrared spectrum is characteristic of the entire molecule, it turns out certain groups of atoms giving rise to bands at or near the same frequency regardless of the structure of the rest of the molecule. It is the persistence of these characteristic bands that permits obtaining useful structural information by simple inspection and reference to generalized charts of characteristic group frequencies.

The fact that many functional groups can be identified by their characteristic vibration frequencies makes the IR spectrum the simplest and often the most reliable method of assigning a compound to its class. IR spectroscopy is most frequently used as a fingerprinting device. The complexity of the IR spectrum lends itself particularly well
this purpose and such comparisons are very important in the complete identification of many compounds.

IR spectra may be measured in an automatic IR spectrophotometer either in solution (in chloroform or carbon tetrachloride 1-5%), as a mull with nujol oil or in the solid state mixed with KBr.

6.4.5. Calibration

The IR spectrophotometer should be calibrated so that the bands are observed at their proper frequencies or wavelengths. Proper calibration can be made with reliable standards such as polystyrene film.

6.4.6. Advances

Earlier dispersive spectrophotometers, introduced in the mid – 1940s were widely used, since they provided the robust instrumentation required for the extensive application of this technique. Now days, fourier transform spectrophotometers have replaced dispersive instruments for most applications due to their superior speed and sensitivity. They have greatly extended the capabilities of infrared spectroscopy and have been applied to many areas that are very difficult to nearly impossible to analyze by dispersive instruments. Instead of viewing each component frequently sequentially, as in a dispersive IR spectrophotometer, all frequencies are examined simultaneously, in Fourier Transform Infra Red (FTIR) spectroscopy.

Photoacoustic spectroscopy (PAS) is a useful extension of IR spectroscopy and is suitable for examining highly absorbing samples that are difficult to analyze by conventional IR techniques.
5. NON-SPECTRAL METHODS USED FOR CHARACTERIZATION DURING PREFORMULATION (Physical Methods)

6.5.1. Determination of Density

The bulk density of the solid is often very difficult to measure since the slightest disturbance of the bed may result in a new bulk density. Moreover, it is clear that the bulking properties of a powder are dependent on the "history" of the powder (e.g., how it was handled), and that it can be packed to have a range of bulk densities. Thus, it is essential in reporting bulk density to specify how the determination was made. Because the inter-particulate interactions that influence the bulking properties of a powder are also the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of relative importance of these interactions in a given powder. Such a comparison is often used as an index of the ability of the powder flow. The bulk density often is the bulk density of the powder "as poured" or as passively filled into a measuring vessel. The tapped density is a limiting density attained after "tapping down", usually in a device that lifts and drops a volumetric cylinder containing the powder a fixed distance.21

6.5.2. Bulk Density21

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder (Method I) or through a volume-measuring apparatus into a cup (Method II).

Method I: Measurement in a Graduated Cylinder

Procedure: Unless otherwise specified, pass a quantity of material sufficient to complete the test through a 1.00-mm (No.18) screen to break up agglomerates that may have formed during storage. Into a dry 250-mL cylinder introduce, without
impacting, approximately 100 gm of test sample, $M$, weighed with 0.1% accuracy. It is not possible to use 100 gm the amount of the test sample and the volume of the cylinder may be modified and the test conditions specified with the results. Select a sample mass having an untapped apparent volume of 150 to 250 mL. A 100-mL cylinder is used for apparent volumes between 50 mL and 100 mL. Carefully level the powder without compacting, if necessary, and read the unsettled apparent volume, $V_0$, to the nearest graduated unit. Calculate the bulk density, in gm/mL, by the formula

$$\text{Bulk/Fluff density} = \frac{(M)}{(V_0)} \text{gm/mL} \quad (6.4)$$

Generally replicate determinations are desirable for the determination of this property.

6.5.3. Tapped Density$^{21}$

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume is observed. The mechanical tappings are achieved by raising the cylinder and allowing it to drop under its own weight a specified distance by either of two methods as described below. Devices that rotated the cylinder during tapping may be preferred to minimize any possible separation of the mass during tapping.

Method I

**Procedure:** Unless otherwise specified, pass a quantity of material sufficient to complete the test through a 1.00 mm (No. 18) screen to break up agglomerate that may have formed during storage. Into a dry 250-mL glass graduated cylinder (readable to 2 mL) weighing 220 (±44) gm and mounted on a holder weighing 450 (±10) gm introduce, without compacting, approximately 100 gm of test sample, $M$,
weigh with 0.1% accuracy. If it is not possible to used 100 gm, the amount of the test sample may be reduced and the volume of the cylinder may be modified by using a suitable 100-mL graduated cylinder (readable to 1 mL) weighing 130 (±16) gm and mounted on a holder weighing 240 (±12) gm.

The modified test conditions are specified with the results. Carefully level the powder without compacting, if necessary, and read the unsettled apparent volume, \( V_o \), to the nearest graduated unit.

Mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester that provides a fixed drop of 14 ±2 mm at a nominal rate of 300 drops per minute. Unless otherwise specified, tap the cylinder 500 times initially and measure the tapped volume \( V_a \), to the nearest graduated unit. Repeat the tapping an additional 750 times and measure the tapped volume, \( V_b \), to the nearest graduated unit. [NOTE: Fewer taps may be appropriate, if validated for some powder]. If the difference between the two volumes is less than 2%, \( V_b \) is the final tapped volume, \( V_t \). Repeat in increments of 1250 taps, as needed, until the difference between succeeding measurements is less than 2%. Calculate the tapped density, in gm per mL, by the formula

\[
\text{Tapped density} \, = \, \frac{(M)/(V_t)}{\text{gm/mL}} \tag{6.5}
\]

Generally replicate determinations are desirable for the determination of this property.

Method II

Proceed as directed under Method I except that a suitable mechanical tapped density tester that provides a fixed drop of 3 mm (±10%) at a nominal rate of 250 drops per minute is used.
6.4. Measurement Of Powder Compressibility

The Compressibility Index and Hausner Ratio are measures of propensity of a powder to be compressed. As such, they are measures of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio.

6.4.1. Compressibility Index: Calculate by the formula

\[ 100 \frac{(V_o - V_t)}{V_o} \]  
(6.6)

6.4.2. Hausner Ratio: Calculate by the formula

\[ \frac{V_o}{V_t} \]  
(6.7)

6.5. Flow Property

A bulky powder is somewhat analogous to a non-Newtonian liquid, which exhibits plastic flow and sometimes dilatancy, the particles being influenced by attractive forces to varying degrees. Accordingly powders may be free flowing or cohesive and "sticky". With small particles (less than 10µm); particle flow through orifice is restricted because the cohesive forces between the molecules are often of the same magnitude as gravitational forces. As the particle size increase the in flow is obtained, however, a maximum flow rate is reached after which flow decreases as size of the particles approach that of the orifice.

Powder flow property may be increased by (a) removing the fines and (b) adsorbing them onto larger particles. Occasionally poor flow may result from presence of moisture, in which case drying is beneficial.
Elongated or flat particles tend to pack, albeit loosely, to give powders with a high porosity. Particles with high density and low internal porosity tend to possess free flowing properties. Free flowing powders are characterized by "dustibility". This property can, however, be offset by surface roughness, which leads to poor flow characteristics due to friction and cohesiveness.

A static heap of powder, when only gravity acts upon it, will tend to form a conical mound. One limitation exists: the angle of the horizontal cannot exceed a certain value, and this is known as the angle of repose (\( \Phi \)). If any particle temporarily lies outside this limiting angle, it will slide down the adjacent surface under the influence of gravity until the friction caused by interparticulate forces balances the gravitational pull. Accordingly there is an implied relationship between \( \Phi \) and flow and particle shape. The exact value for \( \Phi \) depends on the method of measurement. The tangent of the angle of repose is equal to the coefficient of friction "\( \mu \)" between the particles.

\[
\tan \Phi = \mu \quad (6.8)
\]

Hence, the rougher and more irregular the surface of the particle, the higher will be the angle of response. Values of \( \Phi \) are rarely less than 20° and values up to 40° indicate reasonably flow rates. Above 50°, however the powder flows only with great difficulty.

**Apparatus:** According to the flow properties of the material to be tested, funnels with or without stem with different angles and orifice diameters are used. The funnel is maintained upright by a suitable device. The assembly must be protected from vibrations. The angle of repose can be calculated using the formula

\[
\tan \Phi = \frac{h}{r} \quad (6.9)
\]
Therefore \( \phi = \tan^{-1}(h/r) \) 

(6.10)

The area of the circle is calculated as

\[
\text{Area of a circle} = \pi r^2
\]

(6.11)

therefore \( r = \left(\frac{\text{area of circle}}{\pi}\right)^{\frac{1}{2}} \) 

(6.12)

Angle of repose has a significant and critical role in tablet manufacture. It governs the properties as (i) fill quantity in the die, (ii) weigh variation, (iii) content uniformity, (v) hardness and (vi) friability etc.

6.5.6. Water Content\textsuperscript{24-25}

The term moisture usually defined as wetness conferred by an unidentified liquid is assumed to be due to water. Moisture in pharmaceutical substance is significant. It affects (i) chemical stability, (ii) crystal structure and (iii) powder flow etc. Process such as wet granulation, mixing extrusion, spheronization, drug loading, tray drying, are some operations, which depend on the amount and state of water present. Moisture can and does influence the properties of individual's active ingredients and excipients and it is essentially, to characterize the effect of moisture on these individual components.

The USP offers two methods for the determination of Moisture Content in solids: (i) Tritrimetry (\textit{Karl Fischer} Titration) and (ii) Gravimetry. Most articles listed in official compendia contain specifications on water or “Loss on Drying”. Since volatile components other than water may be present, “LOD” is no effective moisture content determination technique. These gravimetric techniques recommend use of drying till constant weight under vacuum in oven or modern techniques of infrared or microwave based moisture microbalances.
In its simplest form, Karl Fischer titration is one point determination of moisture content. Its principle advantage are: (i) specificity for water, (ii) it is non-thermal method, (iii) highly sensitive, and (iv) the process can be automated. The main disadvantage is that the solid must dissolve in the titration medium. To be sure that the total amount of moisture is released; however, if analysis carefully designed in such a way that moisture is extracted from the solid to the same degree each time; accurate and reproducible results can be obtained for solids that do not dissolve.

6.5.7. **Particle size and size distribution**

Particle size distribution of drugs, polymer, excipients, granules etc. have profound effect on the mixing phenomenon. Absence of electrostatic charge can result into uniform blends. Particle size also has influence on the dissolution of the drug, which in turn influences the bioavailability. The most common method used to evaluate particle size distribution is optical microscopy, sieve analysis, laser light scattering and electrical zone sensing.

6.5.7.i. **Microscopy**: It is useful as a means to obtain estimations of the particle distribution in a sample. Determination can also be easily made regarding the relative crystallinity and crystallographic information of the material. Evaluation of the morphology of a pharmaceutical solid is also possible, which is of extreme importance, because this property exerts a significant influence on the overall micromeritic and bulk properties of the material. Both optical and electron microscopes are widely used to characterize pharmaceutical solids. Optical microscopy is limited to the range of magnification suitable for routine work, that is, an approximate upper limit of 600X. However, this magnification limit does not preclude the investigation of most pharmaceutical materials, and the use of polarizing optics induces a power into the technique that is not available – with other methods.
Electron microscopy gives excellent three dimensional, topographic and shape of the object.

6.5.7.ii. Sieving\textsuperscript{26-27}: Sieving is one of the oldest methods of classifying powders by particle size distribution. Sieving is most suitable where the majority of the particles are larger than about 75 μm, although it can be used for some powders having smaller particle sizes where the method can be validated. In pharmaceutical terms, sieving is usually a method of choice for classification of the coarser grades of single powders. It is particularly attractive method in that powders are classified only on the basis of particle size, and in most cases the analysis can be carried out in the dry state.

Among the limitation of the of sieving method are: (i) The need for an appreciable amount of sample (normally at least 25 gms), and (ii) Difficulty in sieving oily or other cohesive powders that tend to clog the sieve openings.

The method is essentially a two-dimensional estimate of size because passage through the sieve aperture is frequently more dependent on maximum width and thickness than on length. This method is intended for estimation of the total particle size distribution of a single material. It is not intended for determination of the proportion of particles passing or retained on one or two sieves.

Significant parameters involved in analytical sieving.

(i) The method is generally intended for use where at least 80% of the particles are larger than 75 μm.

(ii) The size parameter involved in determining particle size distribution by analytical sieving is the length of the side of the minimum square aperture through which the particle will pass.
Dry Sieving Method (Method I): Tare each test sieve to the nearest 0.1 gm. Place an accurately weighed quantity of test specimen on the top (coarsest sieve, and replace the lid). Agitate to validated (over established end-point determination) fixed time of sieving.

Interpretation: The raw data must include the weight of test specimen, the total sieving time, and the precise sieving methodology, in addition to the weights on the individual sieves and in the pan. It may be convenient to convert the raw data into a cumulative weight distribution and if it is desired to express the distribution in terms of a cumulative weight undersize, the range of sieves used should include a sieve through which all the material passes. If there is evidence on any of the test sieves that the material remaining on it is composed of aggregates formed during the sieving process, the analysis is invalid.

Sieving procedure is relatively simple, involving mechanical sieve shaker to shake the nest of sieves arranged in descending order. Fraction retained on each sieve is calculated.

6.5. TABLET DOSAGE FORM

6.6.1. Desirable properties of Tablets

- The tablet must be sufficiently strong and resistant to shock and abrasion to withstand handling during manufacture, packaging, shipping and use. This property is measure of two tests: hardness and friability.
- Tablets must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation test and the content uniformity tests.
- The drug content of the tablet must be bioavailable. This property is also measured by two tests: disintegration test and dissolution test. However,
bioavailability of a drug from a tablet, or other dosage form, is a very complex problem and the results of these two tests do not of themselves provide an index of bioavailability. This must be done by monitoring levels of the drug in blood or other bio-fluids.

- Tablets must be elegant in appearance and must have the characteristic shape, color and other marking necessary to identify the product. Markings are usually the monogram or logo of the manufacturer. Tablets often have a code number printed or embossed on the surface of the tablet corresponding to the in-house documentation or as per FDA. Another marking that may appear is to permit breaking the tablet into equal parts for the administration of half tablet. However, it has been shown that substantial variation in drug dose can occur in the manually broken tablets.

### 6.6.2. Tablet Formulation Considerations

- Size of the dose and quantity of active ingredient.
- Stability of the active ingredient.
- Solubility of the active ingredient.
- Density of the active ingredient.
- Compressibility of the active ingredient.
- Selection of the excipients.
- Method of granulation.
- Character of granulation.
- Tablet press, type, size, and capacity.
- Environmental conditions (temperature, dust and humidity control).
- Stability of the final product.
- Bioavailability of the active drug content in the tablet.

The selection of excipients is critical in the formulation of tables. Once the formulator has become familiar with the physical and chemical properties of the drug, the
process of selecting excipients is begun. The stability of the drug should be determined with each proposed excipients.

6.6.3. Techniques for manufacture of extended release tablets

The techniques, equipment and steps involved in manufacturing of immediate release tablets can be used for manufacturing of extended release tablets. Therefore, they enjoy popularity amongst the manufacturer since their manufacturing may not require setting of additional facility.

Extended release tablets can be prepared by compression of granules containing drug and release retarding polymer prepared by any of the following methods.

(i) Granulation  (iii) Microencapsulation and compression
(ii) Hot fusion  (iv) Pelletization and compression

The method used for preparing the controlled released drug delivery system of metoprolol tartrate is by granulation. Hence, this method is taken up for discussion.

6.7. GRANULATION

Most powders cannot be compressed directly into tablets because

(i) They lack the proper characteristics for binding or bonding together into compact entity and
(ii) They do not ordinarily possess the lubrication and disintegrating properties required for tabletting.

For these reasons, drugs must first be pretreated, either individually or in combinations usually with filler and other necessary components to form granules that tend themselves to tabletting. This process is known as granulation.27

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The reasons for granulation:
- Render the material free flowing.
- Densify materials.
- Prepare uniform mixtures that do not separate.
- Improve the compression characteristics of the drug.
- Control the rate of drug release.
- Facilitate metering or volume dispensing.
- Reduce dust.
- Improve the appearance of the tablet.

The principle methods of granulating pharmaceuticals may be classified into three main categories: wet processes, dry processes and other processes. In the wet granulation process, a granulating liquid is used to facilitate the agglomeration process. In the dry granulation process, dry powder particles may be brought together mechanically by compression into slugs or more frequently today, by roller compaction.

Table 6.1. Process used for granulation.

<table>
<thead>
<tr>
<th>General Granulation Process</th>
<th>Specific Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wet</td>
<td>Wet Massing</td>
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<td></td>
<td>Fluid Bed Granulation</td>
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<td></td>
<td>Spray Drying</td>
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<td>Pan Granulation</td>
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<td>Extrusion &amp; Spheronization</td>
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<td>Dry</td>
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<td>Other</td>
<td>Humidification</td>
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<td></td>
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<td></td>
<td>Melt Pelletization</td>
</tr>
</tbody>
</table>

Although some or all these methods are used in the pharmaceutical industry, wet granulation has been and continues to be the most widely used agglomeration process.
3.7.1. Wet Granulation\textsuperscript{30,31}

It is the oldest and most conventional method of making tablets. Although, it is the most labor-intensive and most expensive of the available methods, it continues to persists because of its versatility\textsuperscript{72}.

Granulation is any process of size enlargement whereby small particles are gathered together into larger, permanent aggregates to render them into a free-flowing state\textsuperscript{33}. Size enlargement, also called agglomeration, is accomplished by same method of agitation in mixing equipment or by compaction, extrusion or globulation.

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with a type of agitation that will produce agglomerates or granules. The possibility of moistening powders with a variety of liquids, which also act as carriers for certain ingredients, thereby enhancing the granulation characteristics, have many advantages.

**Fundamentals of Wet Granulation Technique**

6.7.2. Binding Agent\textsuperscript{34}:

Solution of the binding agent is added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has consistency of damp snow or brown sugar. If the granulation is over-wetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.
6.7.3. Granule Drying:\textsuperscript{34}

In drying granulations, it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to maintain the various granulation ingredients, such as gums, in hydrated state. Also, the residual moisture contributes to the reduction of the static electric charges on the particles. In the selection of any drying process, an effort is made to obtain uniform moisture content. In addition to the importance of moisture content in granulation, it's handling during the manufacture steps, the stability of the products containing moisture-sensitive active ingredients may be related to the moisture content of the products.

6.7.4. Sieving:\textsuperscript{34}

After drying, the granulation is reduced in particle size by passing it through a smaller-mesh screen. Following dry screening, the granule size tends to be more uniform. For dry granulations the screen size to be selected depends on the diameter of the punch. For example, tablets of 7/16\textsuperscript{th} inch and larger, use 12 mesh is suggested.

6.7.5. Lubrication:\textsuperscript{32}

Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and polyethylene glycol (PEG). Most lubricants with the exception of talc, are used in concentrations below 1%. When used alone, talc may require concentrations as high as 5%. Poor selection or excessive amounts can result in waterproofing and/or delayed dissolution of the drug substance.

The addition of proper lubricant is highly desirable if the material to be tabletted tends to stick to the punches and dies. Immediately after compression, most tablets have
the tendency to expand and will bind and stick to the side of the die. The choice of
the proper lubricant will overcome this effectively.

The method of adding a lubricant to a granulation is important if the material is to
perform its function satisfactorily. The lubricant must be divided finely by passing it
through a 60–100 mesh nylon cloth onto the granulation (- bolted i.e., dusted through
this nylon clothe over the granules, to eliminate small lumps as well as increase the
covering power of the lubricant). The granules are gently tumble mixed to distribute
the lubricant and without breaking them down to finer particles.

Many formulators once believed (and some still believe) that over-blending resulted
in increased amounts of fines and hence, caused air entrapment in the formula. The
capping and laminating of tablets associated with over-blending lubricants is thought
to be caused by these air pockets. Most scientists now recognize that a plausible
explanation has to be with the function of the lubricants themselves. Since the very
nature of the lubricant tends to make surface less susceptible to adhesion, over-
blending affects compaction.

Selection of Granule Sieve Fraction\textsuperscript{34}:

It has been claimed that too much fine powder is not desirable because fine powder
may not feed into the die evenly; consequently, variations in weight and density
result. Fine powders, commonly designated as fines, also blow out around the upper
punch and down past the lower punch, making it necessary to clean the machine
frequently. Fines however at the level of 10 to 20\%, traditionally are sought by the
tablet formulator. The presence of some fines in necessary for the proper filling of
the die cavity. The flow diagram involving typical steps in wet granulation is given in
Fig.6.1.
6.7.7. Advantages of Wet Granulation

- The cohesiveness and compressibility of powders is improved due to the added binder that coats the individual powder particles, causing them to adhere to each other so that they can be formed into agglomerates called granules. Lower pressures are needed to compress tablets that enhances tool-life and decreases machine wears.

![Diagram of Wet Granulation Process]

Fig. 6.1. Processing steps in Wet Granulation.
Drugs having a high dosage and poor flow and/or compressibility must be granulated by the wet method to obtain suitable flow and cohesion for compression.

- Good distribution and uniform content for soluble, low-dosage drugs and color additives are obtained if these are dissolved in the binder solution.
- A wide variety of powders can be processed together in a single batch.
- Bulky and dusty powders can be handled without producing a great deal of dust.
- Wet granulation prevents segregation of components of a homogeneous powder mixture during processing, transfer and handling.
- The dissolution rate of an insoluble drug may be improved by wet granulation with proper choice of solvent and binder.
- Controlled granulation can be accomplished by the selection of a suitable binder and solvent.

6.7.8. Limitations of Wet Granulation

- Because of the large number of processing steps, it requires a large area with temperature and humidity control.
- Requires a number of pieces of expensive equipment.
- Time consuming, especially the wetting and drying steps.
- Possibility of material loss during processing due to the transfer of material from one unit operation to another.
- Greater possibility of cross-contamination than with the direct-compression method.
- Presents material transfer problems involving the processing of sticky masses.
- Cannot be complete aqueous process, in case of hydrophilic polymer matrix.
During recent years some advances have been made to improve the traditional wet granulation method and reduce its cost. These include:

- Development of high precision automatic systems to determine the end point of the granulation process.
- Design of granulation units in which the whole process of solid-solid mix, liquid-solid kneading, and drying can be completed in one unit.
- Design of fluidized-bed granulators by adaptation of a spray nozzle to fluidized-bed dryers to add the binder. These systems are examples of control granulation to obtain uniform agglomerates. Granulation and drying are carried out simultaneously.
- Development of high speed or shearing mixtures, which provide efficient and quick solid-solid and solid-liquid blending, reducing time and material handling.
- Development of extrusion techniques as a special wet granulation method using more binder liquid and there the end product exhibits higher bulk density. Specific equipment is used because of different rheologic characteristics of the wet mass caused by higher wetting.
- A recent innovation in wet granulating, which reduces the time and energy requirements by eliminating the drying step, is the melt process. This method relies on the use of solids having a low softening or melting point which, when mixed with a powder formulation and heated, liquefy to act as binders\textsuperscript{35-36}. Materials used as binders are polyethylene glycol 4000 and polyethylene glycol 6000\textsuperscript{37-38}, stearic acid\textsuperscript{39}, and various waxes\textsuperscript{40-41}.
- A new variation of the granulating process known as "moisture-activated dry granulation"\textsuperscript{42} combines the efficiency of dry blending with the advantages of wet granulation. As little as 3% water produces agglomeration. The process requires no drying step because any free water is absorbed by the excipients used. After
granulation, disintegrant and lubricant are added and the granules are ready for compression\textsuperscript{42-43}.

6.8. TABLET COMPRESSION OPERATION

Tablets are made by compressing a formulation containing a drug or drugs with excipients on stamping machines called Tablet Compression Presses. Tablet machines are designed with the following basic components:

(i) Hopper for holding and feeding granulation to be compressed.
(ii) A feeding mechanism for moving granulation from the hopper into the dies.
(iii) Dies that define the size and shape of the tablet.
(iv) Punches for compressing the granulation within the dies.

Tablet presses are classified as either single punch or multi-station rotary presses. Single punch machine gives one compression per cycle. Since only upper punch is involved in the compression, tablets produced in these machines may have inferior uniformity of compactness. Multi-station presses are termed rotary because the head or turret of tablet machine that holds the upper punches, dies, and lower punches in place, rotates. As the head rotates, the punches are guided up and down by fixed cam tracks, which control the sequence of filling, compression, and ejection. Compared to single punch, the rotary presses are known for their high speed and better compaction. This is due to smoother movement of punches and involvement of both upper and lower punches in compression. Rotary machines also deliver tablets, which have better reliability and reproducibility. These machines are very versatile, and have been modified to produce various novel tablet forms such as dry coated, multi-layered and special delivery type dosages.
9. OPTIMIZATION

The optimization of pharmaceutical formulation with regards to one or more attributes has always been a subject of importance and attracts attention of those engaged in formulation research. Product formulation is often considered an art. The pharmaceutical scientist has, therefore, the responsibility to choose formulation whose attributes conform to certain predefined requisites. The word "optimize" is defined as "to make as perfect, effective or functional as possible"\(^4\). The word "optimization" is used in pharmacy with respect to standardization of formulation and to processing condition.

6.9.1. Optimization of Tablet Dosage Form

In extended release tablets as in conventional tablet formulation, optimization of all formulations and processing conditions is necessary to obtain an effective optimum product.

Optimization involves:
- Drug properties and excipients like particle size and distribution, crystal nature, bulk density and moisture content, to name a few. Type and concentration of excipients like retarding polymer, binders, lubricants etc.

6.9.2. Process and Equipment Optimization

- **Mixing:** Mixer type, mixing time, mixing speed, vessel capacity and load.

- **Drying:** Drying time, temperature, drying load, heat and air circulation in dryer, determination of cold spots, nature of inlet air in terms of quality, temperature, humidity, type of dryer (fluid bed dryer\(1\)/tray dryer\(1\)/infrared dryer etc.).

- **Lubrication:** Time of mixing, type of mixer. These have a profound effect on the disintegration and dissolution properties of the formulation.
**Compression:** Hardness, flow through hopper, speed of compression, thickness of tablets, shape of tablets etc. Each of these has some say in either the availability of drug (hardness), content of drug in dosage form (flow through hopper) or in packing (thickness and shape).

Optimization studies in table granulation have been studied by many workers via factorial design using various aspects like (a) type of mixers viz., Diosna mixer and Planetary, indicated that impeller speed, the moisture content of starch and added amount of water; (b) in Fluid Bed Granulator – inlet air temperature, air volume, spray gun number, height from bed, atomization, air pressure, spray rate significantly influences the response variable, i.e., granule size and size distribution. They also found that drug concentration, excipient and binder, solvent nature; all influence the response variables. In controlled release formulation, optimization becomes much more critical as it may have drastic effects on drug release profile. In addition to the usual tablet properties, studies of pharmacokinetic parameters such as time to reach plasma concentration, lag time, absorption and elimination rate constants have also been optimized.

For the present work, tableting by the process of wet granulation mixer was planned with an intension of optimization and scale up to product level.

**6.9.3. Granules Evaluation**

The granules produced after granulation are evaluated for appearance, loss on drying, particle size distribution, flowability and derived properties such as Carr’s Index as per procedures reported in the chapter.
6.9.4. Tablet Evaluation

6.9.4.i. General Appearance

The general appearance of a tablet, its visual identity and overall "elegance", is essential for consumer acceptance, for control of lot-to-lot uniformity and general tablet-to-tablet uniformity, and for monitoring trouble-free manufacturing. The control of the general appearance of the tablet involves the measurement of number of attributes such as tablet's size, shape, color, pressure or absence of odor, tastes, surface texture, physical flaws and consistency, and legibility of any identifying marking.

6.9.4.ii. Size & Shape

A compressed tablet's shape and dimensions are determined by tooling during the compression process. The thickness of a tablet is the only dimensional variable related to the process. The crown thickness of individual tablets may be measured with a micrometer, which permit accurate measurement and provides information on the variation between tablets. Tablet thickness can be controlled within ± 5% variation of a standard value. The physical dimensions of the tablet, along with the density of the materials in the tablet formulation and their proportions, determine the weight of the tablet.

6.9.4.iii. Unique Identification Markings

These markings utilize some form of embossing, engraving, or printing. The type of informational markings placed on a tablet usually includes the company name or symbol, a product code, the product name, or the product potency.
5.9.4.iv Organoleptic Properties\textsuperscript{46, 47-50}

- **Color:** The color of a product must be uniform within single tablet from tablet to tablet, and from lot to lot. Efforts to quantitate color evaluations have used reflectance spectrophotometry, trimulus colorimetric measurements, and the use of a microreflectance photometer to measure the color uniformity and gloss on a tablet surface. Many pharmaceutical tablets use colors as a vital means of rapid identification and consumer acceptance.

- **Odor:** Odor could be characteristic of the drug or formulation. But the presence of an off odor in a batch of tablets could indicate a stability problem, or could be characteristic of the drug in the dosage form.

- **Taste:** Taste is important in consumer acceptance of chewable and certain other tablets.

A tablet's level of flaws such as chips, cracks, contamination from foreign solid substances, surface texture and appearance may have a zero-defect specifications, but the visual inspection technique used for detecting or evaluating these characteristics are subjective in nature. Electronic devices that are currently being developed hold promise for making inspection a more quantitative and reproducible operation.

6.9.4.v. **Mechanical Strength**\textsuperscript{51, 52-56}

The mechanical strength of a table is associated with the resistance of the solid specimen towards fracturing and attrition. An acceptable tablet must remain intact during handling between production and administration. This, an integral part of the formulation and production of tablets is the determination of their mechanical strength. Such testing is carried out for several reasons, such as:
(i) To assess the importance of formulation and production variables for the resistance of a tablet toward fracturing and attrition during formulation work, process design and scaling up;

(ii) To control the quality of tablets during production (in-process and batch control);

(iii) To characterize the fundamental mechanical properties of materials used in tablet formulations.

The most commonly used methods for strength testing can be subcategorized into two main groups: (i) attrition-resistance methods and (ii) fracture resistance methods.

**Attrition-Resistance method:** The idea behind attrition resistance methods is to mimic the kind of forces to which a tablet is subjected during handling between its production and its administration. These are also referred to as friability tests: a friable tablet is one that is prone to erode mechanically during handling. During handling, tablets are subjected to stresses from collisions and tablets sliding towards one another and other solid surfaces, which can result in the removal of small fragment and particles from the tablet surface. The result will be a progressive reduction in tablet weight and a change in its appearance. Such attrition can occur even though the stresses are not high enough to break or fracture the tablet into small pieces. Thus, an important property of a tablet is its ability to resist attrition so as to ensure that the correct amount of drug is administered and that the appearance of the tablet does not change during handling. Another application of a friability method is to detect incipient capping, as tablets with no visible defects can cap or laminate when stressed an attrition method, e.g., a rotation cylinder.

- Normally, weight loss of less than 1% during friability test is required. In addition, the tablets should not show capping or cracking during such testing.
Fracture resistance methods: Analysis of the fracture resistance of tablets involves the application of a load on the tablet and the determination of the force needed to fracture or break the specimen along its diameter. The force needed for fracture of a tablet depends on the tablets dimensions.

For a cylindrical flat-faced tablet, the tensile strength \( (\sigma_t) \) can be calculated by equation (6.12)

\[
(\sigma_t) = \frac{2F}{\pi D_t}
\]  (6.13)

where \( F \) is the force needed to fracture the tablet and \( D \) and \( t \) are the diameter and the thickness of the cylindrical flat-faced tablet, respectively.

6.9.4.vi. Hardness

The tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacturing, packaging and shipping. In addition, tablets should be able to withstand reasonable abuse when in hands of the consumer, such as bouncing about in a woman’s purse in a partially filled prescription bottle. Adequate tablet hardness and resistance are requisites for consumer acceptance.\(^46\)

6.9.4.vii. Friability\(^57\)

For a tablet with a unit mass equal to or less than 650 mg, take a sample of whole tablets corresponding to 6.5 gm. For tablets with a unit mass of more than 650 mg take a sample of 10 whole tablets. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh.

- If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If the results are doubtful or if the weight loss is greater than the targeted value, the test should be repeated twice and the
mean of the three tests determined. A maximum weight of the tablets being tested is considered acceptable for most products. In the case of new formulations, an initial weight loss of 0.8% would be permitted until sufficient packaging data are obtained to extend the limit to a targeted value of 1%.

- If the tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about $10^\circ$ with the bench top and the tablets no longer bind together when lying next to each-other, which prevents them from falling freely.

- In case of hygroscopic tablets, humidity – controlled environment (relative humidity less than 40%) is required for testing.

6.9.4.viii. Disintegration

This test is provided to determine compliance with the limits on Disintegration stated in the individual monograph except where the label states that the tablets or capsules are intended for use as troches or are to be chewed, or are designed as modified-release dosage forms.

- Disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragment of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

6.9.4.ix. Uniformity of Dosage Units

The uniformity of dosage units can be demonstrated by either of two methods, weight variation or content uniformity. And the relative standard deviation (RSD) was calculated using the formula

$$s = \left[ \frac{\sum (x_i - \bar{x})^2}{n-1} \right]^{1/2}$$

(6.14)
and

\[ RSD = \frac{100s}{X} \]  

(6.15)

where \( s \) = sample standard deviation, \( RSD \) = relative standard deviation (the sample standard deviation expressed as a percentage of the mean), \( \bar{X} \) = mean of the values obtained from the units tested, expressed as a percentage of the label claim/ strength of the formulation, \( n \) = number of units tested, \( x_1, x_2, x_3,... x_n \) = individual values (\( x_i \)) of the units tested, expressed as a percentage of the label claim/ strength of the formulation.

### 6.9.4.x. Weight Variation\(^{59}\)

With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made, is routinely measured to help ensure that a tablet contains the proper amount of drug. In practice, a composite sample of tablets (usually 10) are taken and weighed throughout the compression process as in-process evaluation.

- The Pharmacopoeial weight variation test is done by usually weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average.
- To assure uniform potency of tablets of low dose drugs, a content uniformity test is applied.

### 6.9.4.xi. Drug Content and Release

As mentioned earlier, a physically sound tablet may not produce the desired effects. To evaluate a tablet's potential for efficacy, the amount of drug per tablet need to be monitored from tablet to tablet and batch-to-batch.
6.9.4.xii. In vitro Dissolution Testing

A biopharmaceutical\textsuperscript{60} critical\textsuperscript{61} test method to measuring the performance of the pharmaceutical products and is required by the Compendia. It is an important tool in quality control and an aid in developing pharmaceutical formulations. It measures changes in the stability of the product, and it establishes \textit{in vitro} – \textit{in vivo} correlations\textsuperscript{61}.

Pharmaceutical companies rely heavily on the \textit{in-vitro} dissolution or release test to develop extended-release products and to ensure their performance \textit{in vivo}. Wagner\textsuperscript{62} stated, “future research in dissolution rates should be directed mainly towards establishing correlations of the \textit{in vitro} data with the \textit{in vivo} data”. A strong correlation between the \textit{in vitro} and the \textit{in vivo} results can predict the \textit{in vivo} performance accurately and therefore indicates the tests usefulness as a tool for development and production control. To reach a valid correlation, one has to have valid methods to yield meaningful measurement, both \textit{in vitro} and \textit{in vivo}, according to Extended Release Oral Dosage Forms: Development, Evaluation, and Application of \textit{In vitro/In vivo} Correlations, US FDA\textsuperscript{63}.

6.9.4.xii.a. Objectives In Performing Dissolution Tests\textsuperscript{60}

(i) Investigation of drug release mechanism, especially ER formulations.

(ii) To obtain a predefined target release profile and robust formulation properties regarding influences of physiological factors (e.g., pH and food) on the drug release.

(iii) Generation of supportive data to bioavailability studies as an aid in interpretation of \textit{in vivo} results.

(iv) Validation of manufacturing process.

(v) Investigation of effects of different storage conditions.
vi) Batch quality control (QC).
(vii) A surrogate for bioequivalence studies.

An in vitro dissolution method for batch QC is always defined for a new solid dosage form product. However, this method may not be sufficient for all the different aims of dissolution testing that might arise. The choice of dissolution method and test conditions should therefore be adapted to best serve their purpose. For example, simplicity and robustness are crucial properties of a QC method; whereas physiological relevance may overrule these factors when a method is used for in vivo predictions.

Standard in vitro dissolution testing models two process: (i) the release of drug substance from the solid dosage form and (ii) drug dissolution. Drug release will be determined by formulation factors such as disintegration/dissolution of formulation excipients or drug diffusion through the formulation. Drug dissolution will be affected by the physicochemical substance properties (e.g., solubility, diffusibility), solid-state properties of the substance (e.g., particle surface area. Polymorphism) and formulation properties (e.g., wetting, solubilization). In vitro dissolution testing should thus provide predictions of both the drug release and the dissolution process in vivo. Therefore, in most situations, the use of in vitro dissolution will be meaningless if the method used does not provide some correlation with the in vivo data or resemblance with the physiological conditions in the g.i.t. In order to reach this goal, the choice of dissolution apparatus and test medium should be carefully considered. Another important aspect in the development and definition of a new method is that it must be designed and operated in such a way that drug release and dissolution are not sensitive to minor variations in the operating conditions.
6.9.4.xii.b. Choice of Dissolution Apparatus

The choice of dissolution apparatus will be specific for each formulation, and the following factors should be considered:

(i) Correlation to in vivo data.
(ii) Risk for hydrodynamic artifacts.
(iii) Regulatory guidelines.
(iv) Drug solubility.
(v) Need to change the dissolution medium during dissolution testing.
(vi) Ease of operation, in-house know-how and suitability for automation.

6.9.4.xii.c. Choice of Agitation Intensity

All compendial dissolution apparatus can be operated at different agitation intensities. The three most outstanding aspects to consider when deciding at which level the test should be performed are:

(i) Correlation to the in vivo data
(ii) Variability of dissolution results
(iii) Regulatory Guidelines and Pharmacopoeial Recommendations.

The US regulatory agency recommends a stirring rate of 50-100 rpm, for USP I and 50-75 rpm for USP II.

6.9.4.xii.d. Choice of Dissolution Test Media

The choice of the dissolution medium is highly dependent on the purpose of the dissolution study, but the following aspects should always be considered:

(i) Correlation to in vivo data.
(ii) Resemblance of physiological conditions in the GI tract.
(iii) Regulatory and Pharmacopoeial recommendations.
(iv) Drug solubility and stability properties – at different pH values.
(v) Known sensitivity of the formulation function for different medium factors.

Attainment of IVIVC is a key aspect in the choice of dissolution test medium. However, it is recommended to choose a test medium based only on correlation to in vivo data. The dissolution test medium should also be relevant for the physiological conditions in the GI tract. Another important aspect is selection of sink conditions.

6.9.4.xii.e. Controlled Release Workshop Recommendations for In vitro Tests:

The Controlled Release Workshop\textsuperscript{64} recommends that the in vitro test is desirable for the purpose of (i) providing necessary process control and stability determinations of the relevant release characteristics and (ii) Facilitating certain regulatory determinations and judgments, concerning minor formulation changes, site of manufacturing changes, etc. It recommended:

A. Preparation of at least three dosage formulations with different biopharmaceutic characteristics (change in in vitro dissolution of these test dosage forms being accomplished by changing only these process and component variables that are likely to be varied under normal manufacturing conditions;

B. Development of an appropriated in vitro test capable of distinguishing between these formulations; characteristics of these formulations in a small group of human subjects. The in vitro drug release kinetics of the dosage form intended to be marketed should be characterized as a function of medium pH, rate of agitation, and possibly also medium composition (such as surfactants and bile salts). Since the knowledge of controlled release product IVIVC development and testing is still evolving, alternative approaches to this problem should be explored and should be considered by the Agency on their merits.
The key elements for dissolution are: (i) Reproducibility of the method, (ii) proper choice of media, (iii) maintenance of sink conditions, (iv) control of solution hydrodynamics, (v) dissolution rate as a function of pH ranging from pH 1 to pH 8, including several intermediate values, preferably as topographic dissolution characterization, (vi) selection of the most discriminating variables (media, pH, rotation speed, etc.) as the basis for the dissolution test and specifications.

C. The dissolution procedure should establish (i) Lack of dose dumping – indicated by a narrow limit on the one hour dissolution specifications, (ii) Controlled release characteristics – by employing additional sampling windows over time (Narrow limits with an appropriate Q value system will control the degree of first order release), (iii) Complete drug release – indicated by a 75 – 80 % minimum release specification at the last sampling interval and (iv) and dosage form pH dependence/independence indicated by percent dissolution in water, appropriate buffer, gastric (minus enzyme) and simulated (minus enzyme) fluid.

6.9.4.xii.f. Biopharmaceutical Classification System for Drugs

Amidon et al\(^6\) devised a biopharmaceutical classification system (BCS) to classify drugs on their aqueous solubility and intestinal permeability. It was then recognized that dissolution rate has a negligible impact on bioavailability of highly soluble and highly permeable (BCS I) drugs when their formulations dissolution is sufficiently rapid\(^6\). As a result, various regulatory agencies including the US FDA now allow bioequivalence of formulations of BCS Class I drugs to be demonstrated by in vitro dissolution (often called a biowaiver)\(^67, 68\).
The principles of in vitro drug release can be extended to other dosage forms where the product sameness can be ensured by profile comparison between. In addition, in vitro dissolution/drug release test can also be used for providing biowaivers for low strengths of a product from a given manufacturer, once the higher strength is approved based on the appropriate bioavailability/bioequivalence test procedure.

6.9.4.xii.g. Guidelines And Compendial Specifications

The Division of Bio-Equivalence (DBE) in the Office of Generic Drugs (OGD), FDA, issued a guidance, “Oral extended (controlled) release dosage forms: in vivo bioequivalence and in vitro dissolution testing”. The bio-studies and dissolution testing required to support an ANDA for an ER product are discussed in detail in Section IV. In addition to biostudies and dissolution data, the following are significant:

(i) Although the generic product and the listed reference product must be pharmaceutically equivalent, the mechanism by which the release of active substance occurs does not have to be same.

(ii) The biobatch used for in vivo bioequivalence studies must conform to the OGD Policy and Procedure Guide 22-90.

(iii) The assay potencies of the test and reference products should not differ by more than 5%.

(iv) A single dose, two-way cross over fasting study is required for each strength of a generic ER tablet product. The multiple dose, steady state study and the food study are conducted only on the highest strength.

(v) A single dose, two way crossover fasting study is required for only the highest strength of a generic extended release capsule product, provided that: (a) formula compositions of the lower strength are proportional to that of this highest strength and (b) the capsule contains identical beads or pellets.
Single-dose studies for the lower strengths may be waived on the basis of acceptable dissolution testing. The multiple dose and food studies are to be conducted with the highest strength of the capsule formulation.

A workshop report on controlled/modified release dosage forms\textsuperscript{73} was issued regarding "In vitro and In vivo Testing and Correlation for Oral Controlled/Modified Release Dosage Forms," and recommendations were made concerning which pharmacokinetic studies were needed in several cases. Case III is for generic equivalents of approval extended release products. The generic formulation must be comparable with respect to rate and extent of availability (using the parameters AUC, C\textsubscript{max} (peak concentration), C\textsubscript{min} (trough concentration and fluctuation) to the standard extended release product in a steady-state crossover study. The food studies as described in Case I are also needed. The workshop report also agreed in principle with the USP article on IVIVC\textsuperscript{74} but recognized that separate correlations may be required for each manufacturer's extended release product. The in vitro dissolution method and specifications must be optimized for response to the range of critical manufacturing variables that affect drug release. FDA describes how to apply similarity factor (f\textsubscript{2} calculation) to compare dissolution profiles of different batches to assess or establish bioequivalence\textsuperscript{75-77}.

Dissolution test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form. Where the label states that an article is enteric coated, and a dissolution or disintegration test that does not specifically state that it is to be applied to enteric-coated articles is included in the individual monograph, the test for Delayed Release Articles under Drug Release\textsuperscript{78} is applied unless otherwise specified in the monograph. For hard or soft gelatin capsules and gelatin – coated tablets that does
not conform to the Dissolution specifications, repeat the test as follows. Where water or medium with a pH of less than 6.8 is specified as the Medium in individual monograph, the same Medium specified may be used with the addition of purified pepsin that results in an activity of 7,500,000 Units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL.

6.9.4.xii.h. Drug Release\textsuperscript{78}

This test is provided to determine compliance with drug – release requirements where specified in individual monographs. Use the apparatus specified in the individual monograph. Replace the aliquots withdrawn for analysis with equal volumes of fresh Dissolution Medium at 37 °C or, where it can be shown that replacement of volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.

For ER products labeled to be administered every 12-24 hour, the sampling schedule is: 1 and 2 hour, to ensure lack of dose dumping; 4hour, to establish extended release characteristics; every 2 hour, to establish at least 80 % release. If the release is less than 80 %, dissolution conditions should be changed. In general, the range of release a each sampling time should not exceed 30% with ranges of 20-25% preferred by DBE Specifications for drug release are determined on a case-by-case basis\textsuperscript{79}.

6.9.4.xii.i. Criteria for Acceptance Level\textsuperscript{78}

The individual monograph requirement are met if the quantities of active ingredient (Q) are dissolved from the units tested conform to Acceptance Table 1, shown below.
Table 6.2. Official specification for in vitro dissolution acceptance level for extended release tablets.

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L₁</td>
<td>6</td>
<td>No individual values lies outside the stated ranges and no value is less than the stated amount at the final test time.</td>
</tr>
<tr>
<td>L₂</td>
<td>6</td>
<td>The average value of the 12 units (L₁+L₂) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10 % of the label content outside each of the stated ranges; and none is more than 10 of labeled content below the stated amount at the final test time.</td>
</tr>
<tr>
<td>L₃</td>
<td>12</td>
<td>The average value of the 24 units (L₁+L₂+L₃) lies within each of the stated ranges, and is not less than the stated amount at the final first time; not more than 2 of the 24 units are more than 10 % of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10 % of the labeled content below the stated amount at the final test time; and none of the units is more than 20 % of the labeled content outside each of the stated ranges or more than 20 % of the labeled content below the stated amount at the final test time.</td>
</tr>
</tbody>
</table>

6.9.4.xii.j. Reference Listed Drug

The US FDA Center for Drug Evaluation and Research (CDER), Glossary of Terms, Reference Listed Drug (RLD) defines (CDER, Glossary) as an approved drug product to which new generic versions are compared to show they are bioequivalent. A drug company seeking approval to market a generic equivalent must refer to the RLD in its Abbreviated New Drug Application (ANDA). By designating a single reference drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart.

6.10. SCALE UP OF FORMULATION

Scale up is generally defined as the process of increasing the batch size. Scale up of a process can also be viewed as a procedure for applying the same process to
different output volume. In moving from lab scale to production scale it is sometimes essential to have an intermediate batch size. This is achieved at the so-called pilot scale, which is defined as the manufacturing drug product by a procedure fully representative of and simulating that is used for full manufacturing scale. For a successful scale up a large amount of information on the process during development has to be generated, key parameters need to be identified. Many scale up parameters are non-linear. Process characterization and verification is must for scale up. Robust formulation is prerequisite for scale up.

6.10.1. Scale Up Consideration For Granulation

Granulation or size enlargement of primary particles is carried out in variety of ways. Various mechanisms of granule formation have been described in literature to summarize three mechanisms for granule formation:

- Bridges due to immobile liquid form adhesional and cohesional bridging bonds.
  Thin adsorption layer bonding of fine particles under circumstances.
- Mobile liquids, where interfacial and capillary forces are present.
- Solid bridges formed due to crystallization of dissolved substances drying.

During scale up, the quality of the granules is essential. A change in granule size distribution, final moisture content, friability, compressibility and compactibility may have a strong influence on the properties of final tablet such as hardness, friability, disintegration, dissolution.

Various equipments have been used for wet granulation. Out of these mixer/kneader high shear/ low shear and fluid bed granulator are commonly used.
In case of mixer/kneader, the granulation process can be easily monitored by monitoring power consumption. Key factor here is correct amount and type of granulating liquid. Interpretation of power consumption plots can also be important for optimizing granulation liquid quantity and type. The wet granules are then dried for removal of moisture or solvent usually in fluid bed or tray driers. Drying involves heat and mass transfer. Heat is transferred to the product and mass is transferred as moisture to surrounding gas, and these two phenomena are independent. This free moisture is amount of moisture that can be removed from material by drying at specified temperature and humidity. The amount of moisture that remains associated with material under drying conditions specified is called the equilibrium moisture content (EMC). Therefore, drying air capacity, air distribution through the product is key to drying process and its scale up. Relative humidity and temperature of inlet air have influence on drying air capacity.

6.10.2. Scale Up Consideration For Tabletting

Two important variables such as formulation variables and equipment variables are to be considered during scale up of tabletting process. Material properties such as free flowing, cohesiveness, lubrication - needs to be evaluated for successful scale up batch. Laboratory test such as particle size analysis, bulk density, angle of repose, funnel flow time are used to compare properties of the scale batches.

Tablet properties useful for evaluation of scale up process; tablet weight and hardness; thickness; friability; assay; uniformity of dose, dissolution. Tablet hardness and dissolution are very important.
*Moore et al* have described a mathematical model describing similarity factor, $f_2$. Mathematical fit factor $f_2$ has been accepted by US FDA for comparison of dissolution.

$$f_2 = 50. \log \left[ 1 + \frac{1}{n} \sum R_j - T_j \cdot 100 \right] \quad (6.16)$$

where

- $R_j = \%$ drug release of reference product at each time point $j$
- $T_j = \%$ drug release of test product at each time point $j$
- $n =$ sampling number

Calculation of Similarity factor, $f_2$ based on the dissolution points on two curves one of each of two products is important. A similarity factor value between 50 and 100 indicates that the two profiles are similar.

### 6.11. DRUG RELEASE MECHANISMS AND MODELLING

The quantitative analysis of the values obtained in dissolution/release tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used. In some cases, these mathematic models are derived from the theoretical analysis of the occurring process. In most of the cases the theoretical concept does not exist and some empirical equations have proved to be more appropriate. Drug dissolution from solid dosage forms has been described by kinetic models in which the drug dissolved amount of drug ($Q$) is a function of the test time, $t$, or $Q = f(t)$. Some analytical definitions of the $Q(t)$ function commonly used are zero order, first order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas models. Other release parameter such as, difference factor ($f_1$) and similarity factor ($f_2$) are used to characterize drug release profiles.
6.12. STABILITY TESTING
The term "stability" with respect to a drug dosage form refers to the chemical and physical integrity of the dosage unit to maintain protection against microbial contamination. The shelf life of the dosage form is the time lapse from initial preparation to the specified expiration date. The monograph specifications of identity, strength, quality, and purity apply through out the shelf life of the product.

6.12.1. Routes by which pharmaceuticals degrade

6.12.1.i. Chemical Degradative Routes

- **Solvolysis**: In this type of reaction the active drug undergoes decomposition following reaction with the solvent present.

- **Oxidization**: In pharmaceutical dosage forms, oxidation is usually medicated through reaction with atmospheric oxygen under ambient conditions – a process commonly referred to as oxidation. Many auto-oxidation reactions are initiated by trace amounts of impurities, such as metal ions or hydroperoxides.

- **Photolysis**: Normal sunlight or room light may cause substantial degradation of drug.

- **Dehydration**: Since it is possible that anhydrous compounds may have different dissolutions rates compared with their hydrates, dehydration reactions involving water of crystallization may potentially affect the absorption rates of the dosage form.
• **Racemization**\textsuperscript{97-98}: Enantiomers often have significantly different absorption, distribution, metabolism, and excretion; in addition to differing pharmacological actions.

• **Incompatibilities**\textsuperscript{99}: Chemical interactions frequently occur between two or more components in the same dosage form, or between active ingredient and a pharmaceutical adjuvant, in pharmaceutical formulation.

• **Other chemical degradation reactions**\textsuperscript{100}: Hydration, decarboxylation, pyrolysis, etc.

6.12.1.ii. **Physical Degradative Routes**

• **Polymorphs**\textsuperscript{101-104}: Polymorphs may exhibit significant differences in important physiochemical parameters, such as solubility, dissolution rate and melting point.

• **Vaporization**\textsuperscript{105-106}: Some drugs and pharmaceutical adjuvants possess sufficiently high vapor pressure at room temperature at room temperature that their volatilization through the package component constitutes a major route of drug loss.

• **Ageing**\textsuperscript{107-110}: The most interesting and perhaps the least-reported area of concern about the physical instability of pharmaceutical dosage forms, is generally termed as ageing. In as ER formulation containing a relatively stable drug like lithium salt, consideration of ageing is of prime importance. This is a process through which changes in the degradation or dissolution characteristics of the dosage form are caused by subtle and sometimes unexplained, alterations
in the physicochemical properties of the inert ingredients or the active drug in the dosage form. Since the disintegration and dissolution steps may be the rate determining steps in the absorption of a drug, changes in these processes, as a function of the "age" of the dosage form, may result in a corresponding changes in the bioavailability of the drug product. This is of special significance in ER release dosage forms. Ageing of solids forms can cause a decrease in their in vitro rate of dissolution, and a corresponding decrease in in vivo absorption cannot be assumed automatically.

- **Adsorption**\textsuperscript{111-112}: It is a drug-plastic interaction, which is increasingly being recognized as a major physical problem.

### 6.12.2. Stability Testing in Pharmaceutical Industry\textsuperscript{113}

The ICH Q1A R Stability Testing Guidelines: Stability Testing of New Drug Substances and Products, The European Agency for Evaluation of Medicinal Products Evaluation of Medicines for Human Use, November 2000 is revised version of the ICH Q1A guideline and defines the stability data package for new drug substance or drug product that is sufficient for a registration application within the three regions of EC, Japan, and United States.

The guideline addresses the information to be submitted in registration application for new molecular entities and associated drug products. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or shelf life for the drug product and recommended storage conditions.
• **Stress Testing:** Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved. Stress testing is likely to be carried out on a single batch of the drug substance.

• **Selection of Batches:** Data from formal stability studies should be provided on at least three primary batches of the drug substances. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as, and procedure that stimulates the final process to be used for, production batches. The overall quality of the batches of drug substances place on formal stability studies should be representative of the quality of the material to be made on the production scale.

• **Container Closure System:** The stability studies should be conducted on the drug substances packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

• **Testing Frequency:** For long-term studies, frequency of testing is normally every 3 months over the first year, every 6 months over the second year, and annually thereafter. At the accelerated storage conditions, a minimum of three times points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended.

• **Storage Conditions:** Long term, accelerated, and where appropriate, intermediate storage conditions for drug substances are given below.
Table 6.3.  Storage Conditions\textsuperscript{90}.

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage conditions</th>
<th>Minimum time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term</td>
<td>25°C ± 2°C/60% RH ± 5% RH</td>
<td>12 months</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30°C ± 2°C/60% RH ± 5% RH</td>
<td>6 months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40°C ± 2°C/75% RH ± 5% RH</td>
<td>6 months</td>
</tr>
</tbody>
</table>

"Significant Change" for a drug substance is defined as failure to meet specifications.

6.12.3.  Climatic Zones\textsuperscript{114-118}

As per many authors, the real life climatic conditions should be considered while selecting the stability testing criteria. It was reported that either unsafe drug products reach market or more often than not stable drugs are necessarily discarded. In many countries like USA, the term "controlled room temperature" is used to describe temperatures in the 15-30°C range prevailing in such diverse thermostatically maintained environments as pharmacies, hospitals and warehouses. While designing the product, it appears to be important to identify the climatic conditions prevailing at the place of destination and consumption. For this purpose, the world has been divided into four climatic zones (Table 6.4) to one of which various places of different countries can be assigned.

Table 6.4.  Climatic Zones.

<table>
<thead>
<tr>
<th>Zone</th>
<th>Climatic Zone Definition</th>
<th>Storage Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Temperate Climate</td>
<td>21°C / 45% RH</td>
</tr>
<tr>
<td>II</td>
<td>Subtropical &amp; Mediterranean Climate</td>
<td>25°C / 60% RH</td>
</tr>
<tr>
<td>III</td>
<td>Hot, Dry Climate</td>
<td>30°C / 35% RH</td>
</tr>
<tr>
<td>IV</td>
<td>Hot, Humid Climate</td>
<td>30°C / 65% RH</td>
</tr>
</tbody>
</table>

6.12.4.  Official Stability Considerations\textsuperscript{119}

Each ingredient, whether therapeutically active or pharmaceutically necessary, can affect the stability of drug substances and dosage forms. The primary environmental factors that can reduce stability include exposure to adverse temperatures, light,
humidity, oxygen and carbon dioxide. Five types of stability recognized are shown in the table below:

Table 6.5. Criteria for acceptable level of stability[^19].

<table>
<thead>
<tr>
<th>Type of Stability</th>
<th>Conditions Maintained throughout the Shelf-life of the Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical</td>
<td>Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.</td>
</tr>
<tr>
<td>Physical</td>
<td>The original physical properties including appearance, palatability, uniformity, dissolution, and suspendability are retained.</td>
</tr>
<tr>
<td>Microbiological</td>
<td>Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>The therapeutic effect remains unchanged.</td>
</tr>
<tr>
<td>Toxicological</td>
<td>No significant increase in toxicity occurs.</td>
</tr>
</tbody>
</table>

6.12.5. Program

- **Scope and Goals:** Activities encompassed by the stability program include sample storage of development or production batches, data collection and storage retrieval; physical, chemical and microbiological testing; document preparation for regulatory submission, and package evaluation.

- **Protocols:** FDA Guidelines and ICH Guidelines are detained concerning sampling, storage conditions and specific test parameters for each dosage form. Accelerated testing is generally done more frequently and for a short duration. Generally, real-time data obtained at the label storage conditions on the final formulation in the final packaging configurations are needed for a NDA.

- **Documentation:** the need for adequate documentation of laboratory operations is established not by good science, but also by regulatory requirement.

[^19]: Reference or citation
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