CHAPTER-01

1.1 Introduction

Pharmacy is the professional science and technique of preparing or manufacturing and dispensing drugs. It is a health care profession that links medical sciences with various sciences, so that to ensure the safety and effective use of pharmaceutical drugs or dosage forms. And Pharmacists are the health care professionals who are the experts in the drug therapy and also optimize the usage of medication for the benefits of the patients (A R. G edited Ramington- Phrmacy, 2005).

Pharmaceutics is a branch of pharmaceutical sciences that deals with the process of making a pure drug into a medication. Pure drug could be a new chemical entity (NCE) or old chemical synthetic or natural substance or any other substance having pharmacological effect. A pharmaceutical drug dosage form or mediation is used by the health professionals for the diagnosis, prevention cure or treatment of the diseases. Pharmaceutics scientists make the drug formulations and optimize the dosage forms, so that the delivery of active drug can happen at the required site in an appropriate concentration. In the simple terms, Pharmaceutics scientists convert a pure drug or a chemical substance into a medicine, by designing different formulations and optimizing the dosage forms. Because the drugs are rarely administered in their pure form as they exist and almost always are converted to medicines before administration. The medicine or drug products as they are called officially that varies relatively from a simple solution to complex drug delivery systems by which they are prepared by using the appropriate excipients or additives in the formulations. The type and quantity of particular excipients are very crucial in the design and preparation of the pharmaceutical formulations. Because the excipients used in the preparation of drug formulations have varied and specific pharmacological functions. The various excipients that among many things can be used as diluents or fillers, disintegrants, solubility enhancers or reducers, suspending agents, thickeners, emulsifying agents or surfactants, preservatives, etc. The principle
objective of using these various types of excipients or additives ultimately is to achieve maximum therapeutic response from the medication by modifying the dissolution rate and improving the bioavailability along with the stability and organoleptic properties of a pharmaceutical product (Aulton M.E and Peter York 2001, Gilbert S. Banker and Christopher T Rhodes, 2002).

1.2.1 Oral Solid Dosage Forms:

Medication is required for the diagnosis, prevention and treatments of diseases and for these reason medicines have been used since thousands of years. For the administration of medicines oral route has been the most preferred route of administration, because of its various advantages in addition to patient compliance. Therefore for the formulation scientist preparation of the oral dosage form is the first choice in converting the active pharmaceutical ingredients into the medicines. Tablets are the most routinely used oral solid dosage forms. However, there will be always scope of improvement and optimization of oral dosage forms or developing a new combination of existing drugs for the design of new oral drug products. Such optimizations can be an improvement of efficacy, a reduction of adverse-effects, and development of synergistic or additive effect combination. The prepared formulation of dosage form can be designed to provide constant release of a drug, for longer duration reducing the frequency of administration (B.R Conway 2008, Peter Davies 2009). The tablets can be classified in based on the types like, chewable tablets, buccal tablets, sublingual tablets, fast dispersible tablets and the modified release tablets like, delayed release tablets, etc. Chewable tablets are prepared to be chewed before being swallowed and should therefore does not leave any unpleasant taste effect. The chewable tablets are generally prepared for patients who have difficulty in swallowing. Irrespective of the type of the tablets being prepared the formulation of tablets requires various excipients. Excipients are the inert inactive substances used to prepare or convert pharmacologically active substance into pharmaceutical dosage forms. The excipients are essential components of solid dosage forms especially the tablets and capsules. The commonly used excipients are; the diluents, which act as bulking or filling materials. Binders or adhesive agents hold the powder particles together, during the compaction and compression of tablets.
Disintegrants are incorporated in the tablets to cause the burst or breaking of the tablets. Glidants and lubricants are used to improve the flow of powder or granules for uniform filling and to avoid the sticking of tablets to dies and punches. And if the tablets are chewable some flavors and sweeteners may be incorporated to enhance the aesthetic properties. Therefore, selection of the inactive materials is a critical in achieving the optimized formulation of tablets. The general criteria for the selection of excipients are; it should be physio-chemically inert and stable. Also conformance to the regulatory agency requirements, no interference with the effectiveness of the drug, they should be non-toxic and available commercially at low cost (M.M De Villiers, 2005, H. K Chan and N. Y. K Chew, 2007).

The modern pharmaceutical compressed tablet fabrication is credited to the Englishman Brockendon in 1843. He was granted a patent for a device which initially consisted of a die made by boring a hole through a piece of metal within which powders could be compressed into tablets with the help of two cylindrical punches. In due course of time powered single punch and multiple punch machines appeared. Upon such development some scientist predicted towards the close for the nineteenth century that the modern compressing tablet equipments could revolutionize the oral administration of the solid dosage forms. The real revolution in tablet making can be attributed to the arrival of rotary machines which with their multiple dies and punches could produce tablets at fantastic rates (B. M Mithal, 1997). Compressed tablets offer a number of advantages to the patients as well as the physicians and the pharmacists and that is why their popularity continues to increase. For the patient, a tablet or a capsule is the most convenient form to use. It neither involves measurement of dose nor calls for much effort on the part of the patient. The patient also find it easy to carry tablets and strip packaging have further facilitated this since the accidental breakages of tablet bottles is not a problem now (Rudnic ME, Joseph, 2001).
1.2.2 Advantages and Disadvantages of Tablets Dosage Forms:

The major advantages of compressed tablets as solid dosage forms: (M.M De Villiers, 2005).

- Tablets are most stable pharmaceutical dosage form. They are easy to carry for the patients and bulk the transport can be done safely.
- An accurate drug dosage of the medicament can be administered easily
- Tablets are the most versatile dosage form and can be prepared in different types and still new formulations are being developed continuously
- The drug release rate from the tablet dosage form can be manipulated as per the pharmacological requirements of immediate or sustained release
- Tablets can be manufactured on a large scale easily and quickly. Therefore, the overall manufacturing cost will be reduced.

1.2.3 The major disadvantages of compressed tablets:

- When the dose is large and the patients, who have difficulty in swallowing a tablet, especially pediatrics and geriatrics, could not take the medication, especially when the drug action is required immediately. Because the disintegration and dissolution of the drug from the tablet could become a rate limiting process.
- During the manufacture of tablets, the impact of the compression force applied can change physical characteristics of the drug.
- In some cases, the organoleptic and the physicochemical properties of the drug could make it difficult to compress the drug as tablet dosage form (Rubinstein MH., 2000, De Villiers, 2005).

1.2.4 Ideal Requirements of a Tablet dosage form:

1. A pharmaceutical tablet should be an elegant product with an appropriate shape with suitable size
2. It should be free from all the tablets defects like, chipping, capping and lamination, etc.
3. It should be stable and should have enough mechanical strength to withstand the attrition and abrasion drug the processing, packaging, shipping and dispensing.
4. It should have both chemical and physical stability to maintain its therapeutic efficacy throughout the self life.

5. It should be able to liberate the active pharmaceutical ingredients in time and get absorbed into the systemic circulation.

6. If the tablet is for buccal or chewable dosage form, it should have good organoleptic characteristics, etc., (P.K. Sahoo 2007).

1.2.5 Stages of Developing the Tablet-Solid Dosage Form:

For every pharmaceutical product or dosage form available in the market in every country, a set of quality control guidelines are specified. The relevant regulatory authorities in different countries, for e.g. Drug Controller General of India (DCGI) in India, FDA in the America, and European Medicines Agency (EMA) in the European countries.

However irrespective of the regulatory agencies guidelines the common six phases of Current Good Manufacturing Practice regulations (cGMP) procedures are required for the development of a new tablet:

1. Development or selection of the active pharmaceutical ingredient (API)
2. Carrying out the preformulation studies, i.e., the characterization of the APIs and the excipients for the pharmaceutical formulation development.
3. Formulation design and optimization of the pharmaceutical product by appropriately selecting the APIs and the excipients.
4. Preparation of the pilot or prototype batches of the optimized formulation
5. Scale up of the optimized pilot batch and the processing steps validation for the manufacturing on the large scale batch
6. Finally performing the quality assurance or quality control tests of the finished products-tablet dosage form (Ingunn Tho and A B-Brandl, 2012).
1.3 Preformulation Studies for Solid dosage forms:

Prior to formulation design and development of a pharmaceutical dosage form, it is necessary to perform the characterization of the both active pharmaceutical agents and the excipients during the preliminary preformulation studies.

Preformulation studies are describe as the process of characterization and optimizing the dosage form or drug delivery system by preliminary evaluation of physicochemical properties of the both active and inactive pharmaceutical substances or agents. A thorough understanding of these physicochemical properties will definitely provide a rationale formulation design and helps in developing good quality pharmaceutical dosage form. In the simplest term, these preformulation studies will ensure that there are no significant barriers to the dosage form product development. The various preformulation steps involve a through determination of the physiochemical parameters of the APIs and the inactive substances involved in the formulation development of the dosage form are:

i. Purity Identification of the drug: Identification of the drug is carried out by performing the elemental analysis using the UV/visible spectroscopy, I.R Spectroscopy and Mass spectroscopy etc.

ii. Development or Establishment of analytical methodology: In the development of the formulation of the dosage form each subsequent property would necessitate the quantitative determination. It is therefore, imperative to develop an quantitative analytical method for assay. Initially, a U.V method with the measurement of $\lambda_{\text{max}}$ is done then HPLC method using suitable stationary phase and the mobile phase in the appropriate ratio is developed and validated.

iii. Evaluation of the Physicochemical properties like:
   a. Solubility
   b. Partition Co-efficient
   c. Determination of logP and logD
   d. Determination of the PKa or Dissociation constant
   e. Determination of the particle size and shape (polymorphism)
   f. Melting Point determination
g. Powder flow properties determination

h. Drug and excipients compatibility studies (Javed Ali et al., 2006).

The physicochemical characteristics or the properties of the active pharmaceutical ingredient and the inert non-active substances are very important in the design of any dosage form. Solubility, stability, and pH can verily affect whether a drug or API can be released readily from a solid dosage form. They are often preferred, due to chemically stable, easier to process, and more convenient to carry than liquid formulations. But when the active pharmaceutical ingredient is in solid form, it needs to get first solublize or dissolve to be in liquid solution. Further in solution it must be chemically stable to get absorbed through the biological membrane. For this reason it is necessary to perform the preformulation studies both in the solid and solution form. (D.H Barich et al., 2005).

When an aqueous solvent contains a solute a solid substance that is in maximum dissolved concentration at room temperature and pressure, it is called a solubility of that substance. When the solubility of the solid particles exceeds its limit and the liquid phase will be in equilibrium with the solid particles it is called as saturated solution. Solubility governs the rate of dissolution (formation of a solution) of the drug. The partitioning of the drug molecules and the calculation of the log P (partition coefficient) of the nonionized form of an active pharmaceutical ingredient is a measure of lipophilicity and the absorption of the drugs from the biological membrane. A simple in vitro measurement of log P value can give an approximate assumption of absorption of a drug from the biological system (T.Florence and D.Attwood 2006). The routinely used experimental procedure for the determination of solubility is by shaking the aqueous suspension in the suitable container till saturation occurs. In this method the active pharmaceutical ingredient is placed in a known volume of water and kept at constant temperature with shaking for 48 hours. Filtrate samples are withdrawn at specified time and the API concentration is determined by either UV spectroscopy or by liquid chromatography. (Ansel H.C et al., 2007). Dissolution of solid dosage form is defined as a process in which a solid substance solublizes in a given solvent i.e. the rate of mass transfer from the solid surface to the liquid phase. Therefore, solubility is a thermodynamic equilibrium process and the dissolution of solids in the liquid phase is a kinetic process. Dissolution rate is defined as the quantity of the solid substance going per unit time into solution.
under specified conditions of temperature, pH and solvent composition and constant solid surface area. Dissolution will be the rate determining step for hydrophobic poorly aqueous soluble drugs, therefore absorption of such drugs is often considered to be the rate limiting step. If the drug is hydrophilic with high water solubility then, dissolution will be rapid and the permeation through the biological membrane will be the rate determining step in the absorption of drug (D. M. Brahmankar and S. B. Jaiswal 1995).

1.4.1 Classification of Solids:

(a) Crystalline solids; also called true solids
(b) Amorphous solids

A crystalline solid exists as small crystals, each crystal having a characteristic geometrical shape. In a crystal, the atoms, molecules are so arranged that in continue, repeating three dimensional patterns called the crystal lattice. Sugar and salt are crystalline solids. An amorphous solid (Amorphous = no form) has atoms, molecules or ions arranged at random and lacks the ordered crystalline lattice. Examples are rubber, plastics and glass. In their disordered structure, amorphous solids resemble liquids (Arun Bhal et al., 2000).

1.4.2 Isotropy and Anisotropy

Amorphous substances are said to be isotropic because they exhibit the same value of any property in all directions. Thus refractive indexes, thermal and electrical conductivities, coefficient of thermal expansion in amorphous solids are not dependent on the direction through which they are quantified. Crystalline substances, on the other hand, are anisotropic and the magnitude of a physical property varies with directions. For example, in a crystal of silver iodide, the coefficient of thermal expansion is positive in one direction and negative in the other. Similarly, velocity of light in a crystal may vary with direction in which it is measured. Thus a ray of light penetrating through a nicol prism splits up into two components, each travelling with different velocity a double refraction (Arun Bhal et al., 2000). In the present time most of the medicinal products manufactured are solid dosage forms. Specifically in pharmaceuticals, solids are diveded into three groups; amorphous, liquid crystalline and solid crystalline. The crystalline solid substance can exist in more than one form like; change in the configuration arrangements of shape of the molecules in the frame of the crystalline network lattice is referred as
polymorphism. The different shape of crystalline substance is termed as polymorphs. Differential scanning calorimetry (DSC) is the novel sophisticated method routinely used for the physical characterization of the active and inactive pharmaceutical ingredients that includes determination of melting point, polymorphism and the crystalline transition phenomena. Thermal gravimetric analysis is another method that allows studying the compatibility of active pharmaceutical ingredients along with multiple excipients. Likewise Fourier transform infrared spectroscopy (FTIR) is an analytical method that is used to have information related to the molecular structure especially the type of functional groups based on the characteristic molecular vibrations that absorb in the IR region. XRD is typically a nondestructive test and is widely used to determine the differences in the crystal structure (i.e., polymorphs), drug with excipients interaction and identifying amorphous form. For determining the residual solvents, headspace analysis is the preferred sampling technique by GC analysis (G. Z. Zhang and D. Zhou 2009, Donnell and Williams 2012).

1.5 Different Classification of Tablets as Solid dosage form: (B. M Mithal, 1997 and De Villiers2005).

(A) Types of Tablets swallowed orally:
1. Conventional Single layer compressed tablets
2. Multiple layer compressed tablets
3. Compressed Mini-Tablets
4. Orally fast disintegrating tablets
5. Chewable tablets
6. Modified Release oral tablets
7. Sugar coated tablets
8. Film and enteric coated tablets
9. Compression coated tablets, etc.

(B) Tablets used in the buccal cavity:
10. Buccal tablets
11. Sublingual tablets
12. Troches or lozenges tablets
13. Dental cone

(c) Tablets administered by other than oral route:
   14. Parenteral Implantation tablets
   15. Vaginal insert tablets

(D) Tablets used to prepare solution:
   16. Effervescent tablet,
   17. Dispensing tablet,
   18. Hypodermic tablet
   19. Tablet triturates

1. **Conventional Immediate Release Tablets:** These are coated or uncoated single layer tablets manufactured by compression. Conventional immediate release tablets are prepared to disintegrate the drug rapidly for both local action and the systemic action. They are prepared by the three general methods; by wet granulation, dry granulation or direct compression.

2. **Multiple Layers Compressed Tablets:** When two or more layer of tablets are compressed to form a single tablet dosage form are called as the multiple layer tablets. The main reason for preparing the bi-layer or multi-layer tablets is to avoid the physicochemical incompatibility.

3. **Oral / Fast Disintegrating Tablets:** Oral or fast disintegrating tablets are designed to disintegrate in less than a minute into a suspension or solution form when comes in contact with the aqueous fluid either in the buccal or in a half cup of drinking fluid. As the tablets are the most widely used solid dosage form and there is always scope for improving the limitations of tablets like, difficulty in swallowing and delay in the onset of action. For this reason, oral or fast disintegrating tablets are rapidly getting popular.

4. **Mini-Tablets:** Mini-tablets are novel single or multiple solid dosage form which are of the size equal to or smaller than 3.0mm in diameter. Mini-tablets have many advantages compared to pellets and granules for example uniform in size and shape
no multiple coating is required. However can be film coated to enhance the stability and require less coating material because of uniform size and shape with robust mechanical properties.

5. **Chewable Tablets:** Chewable tablets are the tablets mostly uncoated tablets, designed and prepared to be chewed in the mouth producing a good taste solid residue by disintegrating in the oral cavity to be swallowed and more importantly donot have any unpleasant taste. Chewable tablets, when chewed or sucked and swallowed, will provide local effect in the gastrointestinal tract, or be absorbed through the GIT for systemic action.

6. **Inlay Tablets:** Inlay tablets are also known as tablets within tablets and are mainly employed to obtain controlled release of medicaments. They are also called as bull's eye tablet. Because the inlay tablets are a kind of layered tablets, where the core tablet is surrounded by the coating material on the three sides and the top surface is completely left open exposed. Suppose if we compress a yellowish core with the white coating material, it will resemble as boiled egg has been cut horizontally.

7. **Modified Controlled Release Oral Tablets:** Modified release drug delivery systems are the drug delivery systems that are capable of providing control over the drug release, that could be of temporal or spatial type or both sometimes. These systems are designed and prepared to control the drug concentration in the body parts. They are for example, sustained release or prolonged release or extended release or delayed release.

8. **Sugar Coated Tablets:** Primary role of coating of the tablet is to provide stability to the tablet and also to produce an elegant, glossy, easy to swallow tablets. Sugar coating is one of the oldest techniques utilized in the Pharma industry to coat the tablets. It is widely utilized especially in preparing multivitamin minerals and very bad organoleptic drugs. The main drawback of the sugar coating of tablet is the increase in the tablet weight upto doubled the weight of uncoated tablet.

9. **Film and Enteric Coated Tablets:** Film coating is presently the most sophisticated and widely used automated technique for the coating of tablet dosage forms. The general objective of the film coating is to provide protection against the atmosphere or masking the bad taste or modified controlled release. The controlled release tablets
could be enteric coated (delayed release) or sustained polymer coated (sustained release). The film coating tablets have many advantages over the sugar coating like, less increase in the weight upto 2-3%, original shape of the tablet is retained, logs or break lines are possible and the process can be automated easily.

10. Compression Coating: Compression coating is a method of thick coating the core tablets, where the coating of the tablet is done by using the tablet compression equipment instead of coating pan. In this method primarily the small core tablet is prepared and then, this core tablet is placed in between the upper and lower coating layers placed in the larger die cavity and compression is done. By this, all the surface of an inner core tablet is completely gets surrounded by the coat layers. Compression coating is mainly used to develop the combination of drugs and to protect the hygroscopic or unstable drug in the core by coating with the stable outer layers.

11. Buccal and Sublingual Tablet: These tablets, as the name indicates, are prepared to be held in the buccal (in the cheek pouch) and sublingually (under the tongue). Generally the drugs which undergo extensive first pass metabolism are prepared by this method. The buccal tablets could be single or bilayer bioadhesive tablets. And the sublingual tablets are small and flat intended to be held under the tongue. These tablets are designed not to disintegrate but undergo dissolution slowly and release the drug.

12. Troches and Lozenges: Compressed lozenges are called troches in the USP. Lozenges are medicated compressed tablets that do not contain a disintegrant and intended to be disintegrate and dissolved slowly in the mouth for providing the local affect. They generally contain gums and honey in the formulation, used to treat the sore throat or to control coughing. The second type of lozenge are designed and prepared for the systemic effect, for example, multivitamin lozenge. Flavors and sweeteners are the integral part of the formulation of lozenges.

13. Dental Cones: These are the cone shaped tablets designed to be kept in the void space or socket formed after the tooth extraction. The main intention of placing the dental cone is to prevent microbial growth in the socket or to reduce bleeding. Dental cones are formulated in such a way either to erode or dissolve slowly within the 20-40 minutes to release the drug in the small volume of serum fluid present.
14. **Parenteral Implantation Tablets:** These tablets are sterile tablets prepared to be implanted or inserted under the skin subcutaneously. Previously it was done by making a small cut and stitching, but nowadays implantation tablets are small solid cylindrical implants approximately 2-3mm in diameter and 3-6mm in length and are supplied with a reloaded plastic syringe attached to the needle. Implantation tablets are normally used for delivering the contraceptives or other hormones for months or years. Implantation therapy is widely used in the veterinary.

15. **Vaginal Tablets:** These tablets are designed and prepared to be inserted into the vaginal tract. V tabs undergo slow disintegration and dissolution to release the drug in the vaginal cavity. Vaginal tablets prepared usually are wide pear shaped to avoid ejection from the vaginal cavity. These tablets are usually astringent, antiseptic and antibacterial used to treat the infection in the vaginal tract.

16. **Effervescent Tablets:** These tablets are compressed effervescent powders. Effervescent tablets are designed and prepared to produce a solution rapidly upon coming in contact with aqueous with the release of carbon dioxide. The tablets are formulated by compressing the drugs with mixture of carboxylic acids such as citric acid or tartaric acid and alkali like sodium bicarbonate. They are instructed to dissolved in a glass of water before administration.

17. **Dispensing Tablets:** Tablets are prepared by the process of compression intended to be added to a specified quantity of water to produce a solution of a given drug concentration. Previously, used to prepare the bulk stock solution of germicide chemicals, that are not for the internal use.

18. **Hypodermic Tablets:** These tablets are sterile tablets intended for preparing the solution for injection and are composed of one or more active ingredients with the water soluble ingredients. These tablets are dissolved in the water for injection prior to injecting by parenteral route. Especially the drugs those are sensitive to water were prepared as hypodermic tablets.

19. **Tablet triturates / Molded Tablets:** These tablets are presently on the verge of extinction. Previously these tablets were prepared using the molds instead of the compression equipment. These tablet triturates are made from the damp mass using the triturate molds that give them the shape of a cylinder. Solidification of the molded

1.6.1 Processing or Methods of Preparation of Tablets Dosage Forms:
The processing or preparation of the tablets is done by the general three methods;

1.6.2 Direct Compression,
1.6.3 Dry granulation and
1.6.4 Wet granulation.

Processing or preparation of the tablets solid dosage forms is a complex process initiating from the judicious selection of drug and excipients in appropriate quantity to proper processing. Irrespective of the method of preparation is used in the preparation of tablets, the appropriate selection of the required excipients is very essential to obtain good efficacy in vivo (Herbert A. Liberman, 1991). In all the three methods of processing or preparation of tablets, initial few steps are common; grinding if required, weighing accurately and passing through the required sieves and mixing or blending. Uniformity of the particle size and blending properly is crucial for the content uniformity of the tablets (Kottke KM, Rudnic ME, 2002).

Three main Methods of Preparations of Tablets are shown below in the figure:
Fig.01 Schematic Representation of the three main Methods of Preparations of Tablets (Courtesy: Ansel’s Pharmaceutical dosage form P237).
1.6.2 Direct Compression

It is the simplest tablet production method. In this process, tablets are compressed directly without preparing the granules of active ingredients and suitable excipients (including, disintegrants, and lubricants). These blends flow uniformly into the die cavities to form the compacts. The method offers several advantages over wet granulation. First and foremost, the process is economical; a very few processing steps are required in direct compression compared to wet granulation. Other manufacturing variables such as the mode of addition of the binder, drying time, etc. are limited. In tablets made from direct compression the particles do not exist in agglomerate form (granules). Hence, upon contact with the dissolution medium, prime particle dissociation is affected. This in turn may result in faster dissolution which may indeed be the single most important factor controlling product bioavailability. Since no moisture is involved in the preparation of the blends for direct compression, the tablets made from this process tend to be more stable than those produced by wet granulation (Mary Kathryn and Edward M, 2002).

The main disadvantage or limitation of direct compression is that, it is not suitable for all the tablets preparation. This technique requires some specific solid properties, like the powder, should have free flowing and compaction properties. In addition, formulation of low-dose drugs by direct compression requires homogeneous mixing for content uniformity. However, several advances have been made in modifying the particle shape and form of some active ingredients and fillers to render them more suitable for direct compression processing of tablets (S.K. Sing and V. Naini, 2007).

Granulation:

Granulation of the active pharmaceutical ingredient using different excipients and binders either by the wet processing method or dry slugging method, the principle is to agglomerate the fine particles or brought together into larger size particles. Granulation or size enlargement is the process of different unit operations or techniques where the particle agglomeration will take place. In the pharmaceutical solid dosage form development, the granulation of the active pharmaceutical ingredient can be carried out either by the dry granulation or the wet granulation method (Bryan J. Ennis 2010).
1.6.3 Dry Granulation:

Dry granulation is the process whereby granules of powder blends are obtained without the use of heat or solvent. This method is usually reserved for those formulations that cannot be processed by either wet granulation or direct compression due to technical or economical reasons. Dry granulation as the name indicates is the dry process of granulation of the solid powder using the high pressure that leads to formation of bonds between the particles. In general two methods are routinely used in the dry granulation in Pharma industry; the first method is Slugging and the second is by Roller compaction. In this both the methods some quantity of the binders can be used to improve the granulation process (Peter York, 2001).

a) **Granulation by Slugging:** is the method of preparing the granules of the powder by employing the hydraulic pressure to form the large compacts by direct compression. In comparison to the tablet compression the slugs formed during the compaction are of less strength and have cracks and voids in the lumps formed. However, similar to the tablet compression the lubricants are added prior to the slugs compression to avoid or reduce sticking to the tablets compression punches and dies. The compressed slugs formed is further broken and passed through the sieves to form the required size granules. The formed granules are further blended with the disintegrants if required and lastly the lubricants are added prior to compression of the tables (Miller R.W, 2010).

b) **Roller Compaction:** The Roller compaction is the most appreciated and therefore widely used method in the Pharma manufacturing for the dry granulation process. In this method the powder is made to pass in between the rollers operating with high pressure. The rollers are cylindrical rotating with high pressure in the opposite direction (Fig. 02). The shape of the rollers may be flat or concave that can produce the plane sheets or thick rectangular lumps of the compacted powder. Likewise in the slugging here also the formed compacted material is blended with required excipients prior to compression as tablets.
Innovations in designed feed screw system are nowadays commercially available roller compactors globally. As shown in the above figure the configuration of these roller compactors can be operated vertically, angled or horizontally. Novel roller compactor machines have been available, featuring catilever roll systems. That is more sophisticatedly designed and offers easier cleaning and also facilitate product and equipment changeability. These systems reduce the human exposure to the hazardous chemicals and dust (P. Kleinebudde, 2004, Miller R.W, 2010).

1.6.4 Wet Granulation:
Wet granulation methods are the most commonly used technique in the manufacture of tablets dosage form. In this method, the addition of a liquid called as the binder solution and, usually, a polymeric solution is added to the powdered starting materials, and a form of agitation to promote lumps formation followed by drying process (Peter York, 2001). Wet granulation In spite of its costly nature, requiring intensive labor, considerable material handling, and costly equipment, wet granulation continues to be the most widely used process for tablet manufacture. Although many of the products currently being formulated by wet granulation could be made by direct compression, existing government regulations would define such changes as major modifications. These modifications would require changes in ingredients, or at least, changes in forms of previously used excipients. Additionally, wet granulation offers several advantages over direct compression. These advantages include: ease of attainment of acceptable content
uniformity (particularly with soluble, low dosage drugs), ability to regulate moisture content of the granulation during the drying cycle, modification of flow characteristics by controlled particle size distribution, and good distribution of color additives. Through proper selection of the granulation solution and the binder, the dissolution rate may be improved (B.R Conway, 2008, Peter Davies, 2009). While there are a numerous ways to achieve the wet granulation in the pharmaceutical industry, but they all have the following basic procedure; (Gokhale and Trivedi, 2010).

In the wet granulation the mixture of APIs and the excipients is converted into good quality granules by appropriately mixing the pre-milled powders after passing through the sieves. The important step in the process of wet granulation is the addition of type and quantity of the binder solution. This damp mass is mixed vigorously in the suitable mixture blender till the granulation end point. Determination of granulation point or end point is a critical in the granules formation. To obtain the quality granules further the damp mass is passed though the required sieves to breakdown the lumps formed into the granules. The wet granules formed are dried in oven at 40-60° for appropriate time till the complete drying takes place. Finally the dried granules are milled in suitable milling equipment and again passed through the required size sieve to obtain the desired size of granules. There are many different types of equipments used in the process of wet granulation, few of the equipments description is given below (Gokhale and Trivedi, 2010).

1.6.4.1 "V" Blenders:
The "V" Blenders are the versatile and efficient mixing and blending machine. In pharmaceutical formulations they are used for the homogeneous mixing and blending of the dry powders. Due to their V-shaped these blenders ensure proper mixing operating at optimum speed. They are used for both the mixing of the powders and the granules with sufficient continuous movement resulting in good quality of powder blend. The design of
the equipment is such it ensure safety (Gokhale and Trivedi, 2010).

Fig. 03 "V" Blender, (Courtesy of Solace Pvt. Ltd.).

1.6.4.2 Planetary Mixers:
The planetary mixer is usually used in the pharmaceutical industry in the preparation of semisolids like ointments and paste. However, they are also used in the R&D formulation and preparation of tablets by wet granulation method. Planetary mixers contain a thick stainless steel mixing bowl, a mixing shaft attached to the blade. The mixing shaft is run or driven by a planetary motor gear (Fig. 03). The mixer blade is rotated when the small planetary gear, which is attached to the mixing blade, is driven in the direction around the ring gear. Hence, in this mixer, both the mixing blade shaft and the mixing blade rotate at the same time simultaneously. The planetary mixer can be operated at a variable speed. The slower speed is generally used to mix powders, and faster speeds are used for the kneading action required during the wet granulation (Gokhale and Trivedi, 2010).
1.6.4.3 High-Shear Mixer Granulators:

The High Shear Mixer Granulator is in real sense the first practical large equipment in the large scale manufacturing of the tablets. It is an exceptionally engineered with perfection. It is capable of doing many processes with an ease required for the formation of granules. It has a small mill so that it can break down the large lumps to ensure the uniformity of the product free from lumps. High Shear Mixer Granulator are also equipped with the granulation end point detector devices, which are used to find the granulation completion time. There are also some sophisticated clean-in-place or CIP and wash-inplace or WIP systems to help operators in the monitoring of the process through the inbuilt camera. With the use of the sophisticated High Shear Mixer Granulator system, rapid granulation with many desirable characteristics is done. For example like, content and particle size uniformity, granulation end point determination easily and no or minimum exposure to the workers during the process is achieved (Gokhale and Trivedi, 2010).
1.6.4.4 Continuous Wet Granulation Process:

To avoid the various manual transfers during the granulation process. An integrated continuous system that connects to different equipments, for example; discharge from the high-shear mixer to the fluid bed is a very common setup used in the Pharma industry. The material handling and operator exposure problems of the multiphase granulation process can be remedied by the continuous granulation process in which the high-shear wet granulation and drying processes are combined into a single step. This approach improves material handling, reduces the possibility of cross contamination and exposure of potentially toxic materials to the workers and the environment. Moreover, it is easy to maintain compliance with good manufacturing practices (GMP) with the continuous granulation process. The continuous granulation process is a very sophisticated process and it is also very costlier which could lead to the increase in the product price. A schematic diagram of the continuous granulation process being operated in the pharmaceutical industry is depicted in the figure below:

Fig. 05 High-Shear Mixer Granulator, (Courtesy of Solace Pvt. Ltd.).
Process variables in the continuous granulation process will play a very important role in the development of final granules. Generally, pharmaceutical formulations are designed and developed in R&D scale granulators and then scaled up to production-scale granulators. Therefore, there is a possibility of major differences occurring between laboratory and production models of granulators in terms of design, shape, size, and geometry of the continuous granulator equipments. These differences could significantly affect the physical and mechanical properties of the granules, which in turn could affect the quality and effectiveness of the final tablets dosage form. Therefore, the understanding of various process parameters is very crucial for the successful technology transfer in pharmaceutical product development (Gokhale and Trivedi, 2010).
1.7 Background

Increased weight or over weight medically known as obesity is a rapidly growing epidemic normally indicated by excessive fat and body mass accumulation to the extent that it will impair the health of an individual by causing different diseases (WHO obesity factsheet, 2013).

Obesity presently with the international classification of disease code E66 is an epidemic. According to WHO, the obesity as a disease is the excessive fat accumulation that is a progressive systemic process with multi-organ manifestations. Once obesity develops in a person, it causes a lot of physical, medical, psychological and social consequences (M. E. J. Lean, 2000).

Body mass index (BMI) is a method of categorizing the overweight and obesity. It is the ratio of weight-to-height, the body mass in kilograms and divided by the square of the height in meters (kg/m²), (WHO obesity factsheet, 2013, Statistics for obesity UK, 2013). Overweight and obesity are the one of the major risk for global deaths. According to a recent World Health Organization data approximately one and half billion adults world over are overweight and half billion adults are obese, respectively, in the world's population. In other words globally thirty five percent of adults are overweight and elevent percent of adults are obese (Sweeting et al., 2014, C Tsigos et al., 2008).

Table-01 The International Classification of adult underweight, overweight and obesity according to BMI (WHO obesity factsheet, 2013).

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI range (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>19 to less than 25</td>
</tr>
<tr>
<td>Overweight</td>
<td>26 to less than 30</td>
</tr>
<tr>
<td>Obese</td>
<td>31 to less than 40</td>
</tr>
<tr>
<td>Obese I</td>
<td>30 to less than 35</td>
</tr>
<tr>
<td>Obese II</td>
<td>35 to less than 40</td>
</tr>
<tr>
<td>Morbidly obese</td>
<td>40 and over</td>
</tr>
</tbody>
</table>
1.7.1 Pathophysiology and Etiology of Obesity:

Obesity is now a chronic epidemic disease with drastic health consequences, which could have an impact on both the psychosocial and physical well-being of an individual. Extreme ratio of BMI is associated to morbidity and mortality. The mechanism of appetite control seems to be willingness to eat even when not hungry if attractive food is available in inductive settings. Most of the people develop obesity because of consuming very high-calorie rich food and not performing the physical activity especially the well to do people seem to be most at risk (Bray et al., 2004, John P et al., 2011).

1.7.2 Obesity-Associated Health Problems:

Obese individuals will in general suffer from the chronic diseases associated with CVS, impaired glucose tolerance or non-alcoholic fatty liver disease. Especially an increased risk of coronary heart disease, stroke, dyslipidemia and type 2 diabetes. Obesity is one of the causes for poor quality of life. Obese people also tend to have chronic anxiety and depression. Other complications associated with obesity include gallstones, cholecystitis, osteoarthritis, obstructive sleep apnoea, gout, complications in pregnancy and some cancers, etc. (Lewis landsberg et al., 2013, Ann Marie 2006, Anders gummesson 2009).

1.7.3 Medication for Treatment of Obesity:

Medication for treatment of obesity can be a useful supportive to diet and exercise to achieve and maintain meaningful weight loss, reduce the health risks and improve the quality of life (Fast facts Obesity, 2009. The various drugs that are used off label for the management of obesity are, phentermine, diethylpropion, fluoxetine, bupropion, venlafaxine and topiramate are effective in reducing upto five percent of body weight if used for at least six months. (George A Bray 2013, National task force, management of obesity, 1996, Louis J et al., 1998, CK Haddock, 2002). But currently, only four drug products are approved by the American food and drug administration FDA for the weight reduction and management of obesity in adults; the approved are orlistat, phentermine-topiramate, lorcaserin and naltrexone-bupropion. Among this four drug products only Orlistat 120mg is approved and registered for the long term management or treatment of obesity and as 60mg dose of orlistat in now approved and available as over
the counter drug (Kakkar and Dahiya 2015). The main hurdle for development of anti-obesity drugs for the pharmacological treatment of obesity seems to be balancing the risk–benefit ratio and, ensuring the safety is of prime importance. Patients who are obese and suffering from various diseases and who are motivated to undertake concurrent lifestyle change may receive health benefits from the pharmacological treatment of obesity. Even a minimum weight loss of even five percent or more will significantly reduce the various health risks in obese individuals. The pace at which the obesity is growing all over the world and especially in the developed countries it is alarming. Many weight management medications and other treatments are regularly being tried. However, the future of the pharmacological treatment of obesity seems to be promising. There are many new antiobesity agents that are under the development stage and the scientists are also rapidly advancing towards the understanding of the mechanism by which the body weight is regulated. At present, the focus of the physicians who are treating the obesity is towards the changing the lifestyle and suggesting the healthier diet for the patients. But in future a comprehensive approach, where in obese patients will have clinical medication therapy along with other therapies to treat the obesity effectively. Overviews of parts of body associated with pharmacological medication effectiveness for obesity and a flow chart for the pharmacotherapeutic management of obesity are depicted in the figures below.
Fig. 07 An overview of central and peripheral parts of body associated with pharmacotherapies for obesity. (Source Ref.; Lisa L. Ioannides-Demos et al., 2011).
Fig. 08 The proposed flow chart of pharmacotherapy for the management of obesity (Pharmacotherapy in the management of obesity, JAMA, 1996).
1.7.4 Depression:

Depression as we all know is a mental disorder that is associated with depressed mood, loss of interest or pleasure, guilt feeling or low self-esteem, less energy, disturbed sleep, less appetite and difficulty in concentration. Moreover, it often comes with the symptoms of anxiety. According to WHO recent estimate depression, is prevalence among 10% of overall world population (Marina Marcus et.al.,2012). Depression and obesity share many common symptoms like, poor self-image, depressed mood, sleep difficulties, sedentary behavior. In adolescents, increased food intake and weight gain was reported during the depression. (Christina J et.al.,2009, Brandon H. Hidaka et al., 2012, Leonore de Wit. et al., 2010 and Albert J Stunkard, et al., 2003). The severely obese individuals are routinely stigmatized in the society, with discrimination and bias being the most common. The consequences of this stigmatization are seemed in the denial of jobs, uncaring by the health care personal, lagging in the education or victimized by the family members. The obese individuals suffer discrimination extensively from the both directly by abusers and indirectly from the isolation and exclusion from the society, leading to psychological distress. In different sectors of life generally the obese individuals have reported leading a poor quality of life in comparison to the lean individuals (Marcus and Wildes 2009, Rebecca M. P. et al., 2014).

Obese patients having both excessive weight and depression have to face multiple goals and challenges, like trying to improve or reduce the weight to take care of their physical health and also psychologically feel better by accepting self body image. So in an effort of feeling better, they often get trapped in a vicious cycle of attempting to reduce the weight by dieting and losing control and binge eating to contrary become more obese. Many pharmacological and psychological treatment approaches have been tried and used in these patients. Some patients can suppress depression in the short term and some seem to be promising in the long term provided a combination therapy is applied (Licinio J & Wong M 2003, Rosenberger and Dorflinger, 2013, Brooke A. Bailer et al., 2014).
1.7.5 Binge Eating Disorder (BED)

Binge eating disorder (BED) according to American Psychiatric Association is defined as an eating disorder. In BED, the patient eat excessively large quantity of food with loss of control in a short gap of time (e.g., within two hours). The food quantity that is for sure, larger than most people would eat, and a sense of feeling of lack of control over eating or how much one is eating (American Psychiatric Association, 2013).

As per the latest fifth Diagnostic and Statistical Manual (DSM-V), for a patient to be considered suffering from the binge eating disorder at least three of the following symptoms should be observed: (1) Bulk calorie reached food raped intake, (2) Eating food even though there is lack of hunger, (3) Eating excessively until feeling of uncomfortably full stomach, (4) Eating in the isolation to avoid the embarrassment, (5) Feeling of distress or guilt and embarrassment after the BED episode, (6) Occurrence of the BED episode at least once a week for three months (B. Rospond et al., 2015, Yijun Liu et al., 2010, B.E. Wolfe et al., 2009). Some studies have found the high level of food cravings especially for the sweets more in obese binge eaters. This is enough to assume overeating in binge eating disorder and that treatment may be required to control this feature that differentiates individuals without binge eating disorder (Longena Ng and C. Davis 2013).

1.7.6 Carving for Excessive Food or Food Addiction in Obese Binge Eaters:

The compulsive excessive overeating or binge eating has many similarities to the drug addiction. The proclaimed reports are based on the similarities of the clinical features of the drug addiction and food addiction a compulsive excessive overeating. Research literatures at different times have reported that food addiction is associated with lifetime mood disorder or depression due to the negative emotional effect. And the palatable food has proven to activate the dopamine release in the CNS, a reward mechanism similar to that happen in the drug addiction (Davis and Carter 2009, Gearhardt et. al., 2012).
The addiction of the food or food dependence can be divided into the three different phases; excessive food intake or binge eating, the withdrawal effect and carving or starvation. Binge eating disorder is a compulsive bulk or excessive calorie reached food intake in a very short period usually in a span of two hours. During the attack of binge eating period, the patients lose their sense of control and unknowingly eat excessive food that they would not do under normal conditions. Bing eating disorder is mainly related to the emotional distress, i.e., depression, disgust or embarrassment. The other two phases of food addiction the withdrawal effect and carving follows respectively when there is less or non-availability of the palatable food when the carving to get the reward is increased. (B. Rospond et al., 2015, Yijun Liu. et al., 2010).

1.7.7 Relationship between Obesity, Depression and Binge Eating Disorder:
Obesity and depression both are shown to prevalent and simultaneously occur with many health problems not limited to coronary heart disease, hypertension, and increased mortality. (Myles S Faith, et al., 2002). Obesity is also associated with significant psychosocial impairment i.e, obese individuals have a very high coexistence of binge eating disorder. Especially, those obese individuals who are seriously trying to reduce the weight were found to be associated with depression and binge eating disorder (John B
It is clinically proven and established that binge eating is triggered by psychological distress caused by boredom, stress, fatigue, and low mood or depression. At least three studies have examined and found that urge or carving for food is extremely high in obese binge eaters in comparison to obese persons without binge eating pattern. These studies have showed that the food carving is correlated to excessive eating in BED and it is not a result of hunger or calorie deprivation (Longena Ng and C. Davis 2013). It is estimated in various extensive literature review studies the high coexisting of both obesity and depression. Let us examine the some facts and the current data about the obesity, depression and the binge eating disorder.

1.7.7.1 Facts and Current data about Obesity and Depression:
- According to the latest WHO survey globally 35% of the population i.e., one out of three persons is either obese or overweight.
- Presently, there are more obese or overweight people in the developing countries than in the developed countries.
- Depression is the most prevalent mental disorder. According to WHO more than 350 million people worldwide are depressed.
- Depression frequently co-exists with obesity.
- There is proven physiological and psychological relationship between obesity, depression and eating disorders.
- There is two way relationship between obesity and depression.
- Imbalance of neuro-chemicals like, dopamaine, serotonin and norepinephrine are involved in the both mood disorder and weight gain.
- Obesity and depression are the important risk factors for various CVS and many metabolic disorders (Stevns et. al., 2012, Marina Marcus et al., 2012).

1.7.7.2 Facts and Current data about Binge Eating Disorder (BED):
- Binge eating disorder is proven to be existing in two percent of people worldwide
- BED patients have significantly higher BMI than people without a history of eating disorder
- The prevalence of BED in obese persons taking treatments ranges form 18-50%
• The negative emotion or depression serves as a trigger for binge eating in the obese BED persons in comparison to the obese persons without Bing eating disorder (R.C. Kessler et al., 2013 and Keats and Wiggins, 2014).

The existence of binge eating among the obese patients is thought to be between 20-40%. This subgroup of obese persons having eating disorder differs from the obese persons without eating disorder in number of ways. Obese binge eaters experience a greater loss of control over eating and that they are not able to stop or control the urge for eating. They have a history of fluctuation of weight and comparatively have severe obesity. Obese binge eaters also have significantly greater psychological distress, especially depression (G. T. Wilson et al., 1993). A literature survey of past forty years showed that there is a pathogenic relationship between obesity, depression and eating disorders. Coexisting of obesity and depression with binge eating has been proven to co-exist. Many, clinical studies have also proved the association between the obesity and the psychological distress or depression and bing eating disorder in the well organized clinical meta-analysis. The results have indicated that there is a bidirectional relationship between the obesity and depression leading to binge eating (F.S. Luppino et. al., 2010, Pokrajac-Bulian et al., 2013). This project was preceded by reviewing the vast literature and taking into consideration of few outstanding studies (the systematic literature survey and clinical meta-analysis) was carried out. After confirming from these studies that, obese individuals with bing eting disordr will have more psychological distress, or bipolar disorder compared to the obese individuals without BED (R. Riener et al., 2006, S.L. McElroy et al., 2013 and V. Ivezaj et al., 2014).

Therefore, treatment of overweight or obese patients with bing eating disorder is required to address and concentrate on the weight reduction. In addition, treatment programmes should also address the psychological distress or depression comorbidity (Devlin MJ, 2001, McElroy SL et al., 2004, Samantha et al., 2009). The pharmacotherapies of combination model that is recommended for the treatment of obese patients with BEDs and depression is depicted in the figure below.
1.7.8 Need of Combination Therapy as Solid dosage forms:

Historically, combination therapy has been the basis for the treatment of critical chronic diseases like infectious diseases or cancer. Presently a combination approach for the treatment of HIV infected patients, a highly active anti retroviral therapy if found very effective and has reduced the mortality rate in the AIDS patients. Using more than single drug as a combination therapy approach has been successfully utilized for the treatment of various chronic disorders like, cardiovascular diseases. Other diseases like the acute syndrome of coronary and pulmonary arterial hypertension are the examples (Wald DS et al., 2009, Mukherjee B and Howard L 2011). Moreover, the use of thiazide diuretics in combination with two or more drugs of blood pressure lowering category is found to produce an additive or synergistic effect in achieving the maximum effectiveness is another example of combination therapy (Colombel JF et al., 2010). Cardiac diseases are often found to be occurring with the co-morbid diseases like, dyslipidemia, hypertension, diabetes, arthritis and hormonal problems, each of these disease is effectively further treated with the combination of different active pharmaceutical compounds (Friedman
HS et al., 2011, Sawakhanda RB et al., 2011). The challenge in developing a new combination drugs therapy especially for the chronic diseases using the new still patented drugs. The economical pressuring of the companies conducting the clinical trials are often influential for rapid showing the result of the product rather than evaluating drug therapy's mechanism of action. However, cancer and many chronic diseases of infection have been in the recent time been in the forefront interest of developing the combination medication therapy. But still it should be acknowledged that many disorders may be benefitted by the drug combination approaches in the future (Ascierto and Marincola, 20011). Obesity is now established as a disease that is associated with many factors like, environmental, behavioural, genetic factors etc., therefore, the single drug therapy approach in general result in an unsatisfactory result outcome.

1.7.8.1 Combination Oral Dosage Forms and Incompatibility:
Generally in the combination drug dosage form in compatibility is usually due to physical or chemical incompatibility of the substances. Physical incompatibility is usually due to immiscibility, insolubility, precipitation or liquefaction of solid materials. These changes that occur as a result of physical incompatibility are usually visible and can be easily overcome by logical formulation manipulation during the preparation or formulation of the pharmaceutical product. The physical incompatibilities may be removed by applying some of the methods like, changing the order of mixing of active and inactive ingredients or preparing the tablets and layered or compression coating tablets (R.M Mehta, 2000).

The above mentioned tablets have many advantages in overcoming the problem of incompatibilities of medicaments and their deterioration due to various factors. Another advantage is that each individual unit can be identified separately. The invent of the novel packaging is revolutionary because not only it helps in conferring identity to each tablet but it also provides a sealed enclosure which protects the tablets from oxygen, moisture, light etc. as well as facilitates its carriage (B. M Mithal, 1997, Ansel H.C et al., 2007).

1.7.8.2 The advantages of combination drug therapy:
1. Enhanced efficacy of the treatment through synergic or additive action
2. Treatment of two or more co-morbid disease conditions is possible
3. Side effect of the one drug can be reduced/counteract, by using other drug in combination
4. Large dose dumping of the single drug can be reduced by combining two low dose drug combination
5. Sometimes other drug side effect could be advantageous as it may provide synergistic or additive effect and
   However, some possible disadvantages could include therapeutic drug interactions, inflexibility of dosing in combination therapy and finally the cost of treatment could increase (B. Halpern et al., 2010).

The recent FDA approval of the combination dosage form Naltrexone and bupropion, Phentermine and topiramate, extended release drug delivery system has acknowledge the fact that a combination pharmacotherapy compared to monotherapy is more effective and beneficial in the management of obesity and controls the food intake or binge eating. This approval has given more encouragement to the researchers and manufacturers, to put more efforts and find the suitable combination pharmacotherapy that will have enhanced efficacy than monotherapy by either synergistic or additive mechanism of action (A N Sweeting et al., 2014, S.K. Billes et al., 2014).
1.8 Objectives of the Research Project:

1. To carry out the extensive review of literature for the planned project work.

2. To perform the Pre-formulation studies including, characterization of the selected drugs and excipients.

3. To develop a HPLC method for the selected single API or combination of APIs.

4. To design and develop the taste masked stable and efficacious dosage form with better patient compliance.

5. To evaluate the different batches developed and optimize the formulation of planned dosage form.

6. Finally to perform the short term stability studies as per the ICH guidelines.
1.8.1 Scope and Significance of the Research Project:

- Tablets as solid dosage form are the most versatile and widely used means of medication. Tablets dosage form contribute almost one third of the total medicines prescribed globally, and are the most favored dosage form both by the patients and the physicians. However, tablets have some limitations like bad odor and taste and also difficulty in swallowing especially for the geriatric and pediatric patients. For this reason always there will be a scope to improve this solid dosage form design.

- In the recent years research has shown that the obesity may cause psychological distress through the negative body image. Occurrence of depression in obesity is the potential contributor of binge eating disorder which is characterized by lack of control on eating leading to excessive eating in a short time.

- Obesity in association with binge eating disorder could be lethal for overly obese patients who are attempting to lose weight. Therefore physicians, who are treating obese binge eaters, are addressing the co-existing depression and or binge eating disorder.

- At present, Orlistat is the only long term drug approved by FDA for the of obesity. Anti-depressants like SSRIs, Venlafaxine and Bupropion have proved efficacy in the treatment of depression and binge eating disorder. But, these medications are currently available in the market only as capsules or tablets dosage form.

- Hence, for this reason there is a wide scope for the new formulation development and optimization of single or combination of drugs for the Treatment of obesity and binge eating disorder.

- Especially, the significance of this project is in developing the novel chewable dosage forms like, Orodispersible mini-tablets, Minitabs-in-Tablet and Press coated tablets. These chewable dosage forms are designed for better patient compliance to enhance the treatment adherence and increase the effectiveness of the dosage regime.
1.9.1 Oral Solid Dosage Forms Planned for the Project:

1.9.2 Chewable Tablets:

Chewable tablets are mostly the non-coated tablets, designed and prepared to be chewed in the mouth that will produce a good tasting fine agglomerates by disintegrating in the buccal cavity that will be easily swallowed and does not leave any undesirable taste. These tablets are formulated and manufactured by compression generally utilizing sweet or non tasting excipients like, sucrose, Sorbitol or Mannitol as fillers and binders along with flavors and colors to enhance their palatability. Chewable tablets when chewed or sucked and swallowed can provide local effect in the gastrointestinal tract, or be absorbed through the GIT for systemic action. Therefore even though some pharmacopeias exempt the chewable tablet from the disintegration test, but all chewable solid dosage form should be prepared ensuring that it should comply with the specified limits in the standard monograph. Especially for the developed chewable tablet it is necessary to match the drug release profile or dissolution test with the existing immediate release solid dosage form. Because generally the chewable tablets could be swallowed even without chewing or sucking, therefore they should be tested for the drug release of the active ingredients and should be matching or comparable with the existing immediate release solid dosage form (USP 32 2010, BP2008 and Ch.Ph.2005).

In practical the evaluation test procedures employed for the chewable tablets must be the same as that specified for the conventional immediate release tablets. This principle fact of the matter is that, there is always possibility that a patient could swallow the chewable tablets without sucking or chewing the tablet even though the label claims to be ‘chewable tablets’. The evaluation test parameters should be almost similar as used for the conventional immediate tablets of the same drug. However because of the non-disintegrating nature of the chewable tablets it would be necessary to modify the test condition like for example, increase the Rounds per minutes of paddle or agitation and increase the testing duration time of the in-vitro dissolution test (Brown C et al., FIP/AAPS Joint Workshop Report: 2011).
1.9.3 Flavouring of a Chewable Tablets Dosage Forms:

Organoleptic qualities of the chewable pharmaceutical product are very crucial for the patient compliance. Sweeteners and flavors used in the chewable tablets are the very important factor to produce palatable patient compliance chewable tablets. Flavor is the complex effect of three components: taste, odor, and feeling factors. It is associated with the feel good factor and of four senses, i.e., seeing, smelling, tasting and feeling. Flavor is a sensation with multidimensional components involving subjective and objective perceptions. The sensory perceptions are both qualitative as well as quantitative and, for this reason, they are difficult to be measured. The flavor of a chewable formulation is a very important characteristic so much that the very success or failure of a chewable pharmaceutical product can be interlinked with the quality of its flavor. The odourific qualities of a product include an initial impact, mouth feels and after effects of the preparation. Until recently the practice was to incorporate some natural flavours such as clove, eucalyptus, lemon, mint, orange, wintergreen etc., in preparations meant for oral administration. But presently the procedure is to evaluate the drug in into pure form with reference to its aroma, basic taste, mouth effects and overall impression (Sohi, et al., 2004, Reiland and Lipari, 2007). Simultaneously the intensity of these fundamental attributes is assessed. In case the drug has unacceptable taste an attempt should be made to mask the taste by various taste masking techniques like microencapsulation by spray drying or spray congealing, ion-exchange, complexation, etc. However, if the taste of the drug is not very bad or alternately if it is to be incorporated in low dose this step may be not required (Sohi, et al., 2004).

Thereafter the various additives should be decided upon keeping an eye on the ultimate flavor of the pharmaceutical product. Sometimes it is possible to select adjuvants that not only mask the bad odour, but which definitely give a good flavor. Then the drug and the adjuvants should be put together to produce samples of the unflavoured product. Some guidelines for the selection of the suitable flavours are shown in the table below.
Table-02 Flavours for masking the various taste (Reiland and Lipari, 2007).

<table>
<thead>
<tr>
<th>Basic taste</th>
<th>Masking Taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweet</td>
<td>Fruits, vanilla, bubble gum, grape, chocolate</td>
</tr>
<tr>
<td>Acid</td>
<td>Lime, lemon, orange, cherry, grapefruit</td>
</tr>
<tr>
<td>Metallic</td>
<td>Mints, berries, grape, marshmallow, gurana</td>
</tr>
<tr>
<td>Bitter</td>
<td>Coffee, licorice, chocolate, mint, grape fruit, cherry, peach, raspberry, orange, lemon, lime</td>
</tr>
</tbody>
</table>

The aldehydes, in general, have a pleasing flavour and can be gainfully employed for flavouring of products for internal use. The benzaldehyde and cinnamic aldehyde are too well known for their desirable odorific qualities. Acetaldehyde has a sherry like odour. Citral is lemon like. Similarly aldehydes in oil of orange are responsible for its top note.

Salty tastes can also be masked by anise, raspberry, etc. Chocolate flavor masks the bitter tastes effectively and may prove useful in covering taste of quinine and other bitter substances. The sharp sensations of materials like ginger and capsicum, if used judiciously, can induce saucy flavours. These flavours are particularly useful in overcoming flat and chalky tastes of hydroxides of aluminum and magnesium. Peppermint and spearmint could be good adjuncts for ginger and capsicum flavours. Unpleasant odours of many drugs can be covered up with aromatic spices in conjunction with fixatives.

For substances with acrid or burning tastes acacia syrup is suitable while lemon syrup is suitable for salty or acidic compounds. Orange syrup goes will for cough syrups having acetates, bromides, citrates, etc. These days a number of flavor enhancers or modifiers are simultaneously used. For instance, monosodium glutamate is considered to be a potential flavor modifier for pharmaceutical preparations. Other commonly used flavour modifier is vanillin. The flavor modifiers often overcome unpleasant tastes making over flavouring unnecessarily (B. M Mithal, 1997).
1.9.4 Immediate Release Tablets:

Among the different solid dosage forms, conventional release tablets are the most widely used oral solid dosage form. The various factors especially the physicochemical and structure on the deformation during the compression are mechanisms that are very critical to the stable and efficacious tablet formation. However, the compression process can be watched through the on-line screening on the computer monitor (Klevan et al., 2010).

For the release of the drug from an immediate release solid dosage form the first step involved is wetting of the tablets or capsules. Depending on the wetting of the solid dosage form the penetration of water will take place, which will cause the breakdown of the solid dosage form into agglomerates. Further, the agglomerates will disintegrate and dissolve to form a solution (Kottke and Rudnic, 2002).

![Diagram of tablet production and disintegration](image)

Fig. 11 A schematic diagram of the common basic steps involved in the production of the tablet (upper arrows), and the disintegration- deagglomeration and drug release from the tablet (lower arrows). (Source: Ingunn Tho and A B-Brandl, 2012).

In the above figure, it is clearly depicted that the immediate release tablet solid dosage form's basic steps of processing and production. On the other reverse side, it is shown that the prepared solid tablet must be disintegrated into granules and get gradually get dissolved it the GIT fluid to be absorbed or penetrated through the biological membrane. In the process of the tablet disintegration, there are several factors that may affect the
release of the drug from the tablet or capsule dosage forms, (Peter Davies 2009).

Fig. 12 virtual diagram of the oral absorption following solid dosage form administration orally.

Among the different factors the rate of water penetration, voids or porosity in the tablet, the processing method employed is crucial for the immediate release of the drugs. The most important crucial step many researchers will ignore during the formulation of the immediate release tablets is that; the tablets (immediate release type) should be first in the solution form to be properly absorbed by the biological membrane. Therefore the first step is the wetting and breakdown into agglomerates or smaller particles that can be easily solubilize to solution form. Apart from the type and quantity of the disintegrant in the conventional immediate release formulation, the method of processing is very crucial in the development efficacious immediate release tablet dosage form (Lachman L et al., 1991).

1.9.5 Fast Disintegrating Tablets:
Tablets are the most used solid dosage form in the world and there is always scope for improving the limitations of tablets like, difficulty in swallowing and delay in the onset of action (Banker and Anderson, 1991 and Habib, W et al., 2000). Over a decade now Fast-disintegrating tablets (FDTs), have gained enormous popularity for better patient compliance and acceptance. FDTs are meant to disintegrate the tablet in less than a minute into a suspension or solution form when comes in contact with the aqueous fluid. FDTs are especially more acceptable and appreciated by people who have difficulty in
swallowing (Ghosh B, and Rajneesh, 2002, DiLiberto, P.G et al., 2004). FDTs ease of administration without water and provide the fast onset of action is also the reason for their gaining popularity in the general population (S.V. Sastry et al., 2000). Fast disintegrating tablets (FDTs) are those tablets that disintegrate in less than a minute into a suspension or solution form when comes in contact with the aqueous fluid. FDTs are especially more acceptable and appreciated by people who have difficulty in swallowing. FDTs have gained enormous popularity for better patient compliance and acceptance. Also, FDTs have proved and shown in the past that if designed and processed properly they have the ability to enhance the efficacy through increasing the bioavailability of poorly aqueous soluble drug through fast disintegration and enhanced the dissolution rate.


![Fig. 13 Fast Disintegrating Tablets Disintegrating image (Courtesy: Alpex Pharma)](image)

### 1.9.6 Mini-Tablets:
Mini- tablets are novel single or multiple solid dosage form which are in the size equal to or smaller than 3.0mm in diameter. Mini-tablets have many advantages compared to pellets and granules for example uniform in size and shape no multiple coating is required. However can be film coated to enhance the stability and require less coating material because of uniform size and shape with robust mechanical properties (Lennartz and Mielck, 1998 and Munday, 1994).
Mini-tablets have many advantages compared to pellets and granules for example uniform in size and shape no multiple coating is required. And mini-tablets can be coated with film to enhance the stability and require less coating material because of uniform size and shape with robust mechanical properties (Bredenberg, S et al., 2003, Munday, D.L., 1994). When mini-tablets are formulated as oral or fast disintegrating they have established in the past that if designed and processed properly they can enhance the efficacy through increasing the solubility and dissolution rate of poorly aqueous soluble drugs (S.S. Biradar et al., 2006).

Fast disintegrating mini-tablets (FDMTs) have the dual advantage; ease of administration because of small size stable tablets and can provide faster action with increase in dissolution rate. Therefore, they are getting popular as novel drug delivery in the pharmaceutical industry (Parkash V, et al., 2011, Aburahma and Hamza, 2011).

**1.9.7 Micro particles / Mini-Tablets Compressed into Tablets:**

Mini-tablets have many advantages compared to pellets and granules for example uniform in size and shape no multiple coating is required. In addition can be coated to enhance the stability and require less coating material because of uniform size and shape with robust mechanical properties. Mini tablets can be either filled into capsules or compressed as tablets Bredenberg et al., 2003 and Munday, 1994). In the recent times fast disintegrating mini tablets are becoming popularized due to their easy swallow ability, and also they have the established in the past that if designed and processed properly they
can enhance the efficacy through increasing the solubility and dissolution rate of poorly aqueous soluble drug (S.S. Biradar et al., 2006).

Further, the tableting of the mini tablets along with microparticles and excipients could be feasible and lucrative technique. In many studies, the tableting of pellets along with excipients is reported to have many drawbacks. And as noted above compared to pellets mini tablets have an advantage both in ease of the production process and physical stability. However the compressibility of the mini tablets will be significantly affected by the type of excipients combination and the binding agent used, that may also affect the release of the drug form the compressed tablet (Rouge et al., 1997, Xin Pan, et al., 2010).

![Fig. 15 A virtual image of microparticles and mini-tablets compressed into a tablet.](image)

Microparticles or microspheres are the small spherical particles with the diameter in the range of 1µm to 1000µm. Microencapsulation techniques are normally used to mask the bitter tasting drugs, enhance the stability, reduce adverse effects, or extend the release of the active pharmaceutical ingredients. Apart from these applications, microparticles have been widely used in the taste-masking of the bitter and ambiguous drugs. The taste-masked microspheres are mixed with other excipients to form orally disintegrating chewable tablets (Jianchen Xu et al., 2008, Malik, K et al., 2011).

The advantage of the compressed mini-tablets is that it does not show any deformation and fragmentation like that of pellets. The physical properties of the mini tablets are very strong thus, making it more stable and resistant to fracturing during the compression process. This tableting of mini-tablets can be used for biphasic drugs containing in the voids between mini-tablets (Carla M. Lopes et al., 2006).
1.9.8 Compression-Coated Tablets:

A compression-coated tablet is a solid dosage form, in which all the surface of an inner core tablet is completely surrounded by coat layers. Compression coating is mainly used to develop the combination of drugs and to protect the hygroscopic or unstable drug in the core by coating with the stable outer layers, (Herbert A. Lieberman et al., 1989). Compression coating is the complete dry procedure that does not require any liquid during the process. Additionally there is no any heating process, leading to free from adhesion problems as seen in the solvent coating process (Hariharan, M., Gupta, 2001). Compression coated or press coated tablets have two parts, internal core and surrounding coat. For preparing or manufacturing the compression, coated tabled a rotary bi-layer tablet compression machine will be more suitable.

![Fig. 16 virtual Model figure of Compression Coated Tablet](image)

The process involves preliminary compression of the optimized core formulation tablet. The core is small core tablet and prepared on a separate turret. To prepare a complete compression coated tablet, a bigger die cavity in another turret is used. In that first the required quantity of coat material is placed in the first feed frame and on that core tablet is mechanically placed and pre-compression is done with less force. And then in the second feed frame the outer coat layer is filled and final compression is done with enough force to get a compression coated tablet. Incompatible drugs may be formulated togeather by this method by taking the one drug in the core and the other drug in the coating
formulation. By applying the compression coating there is possibility of two-release pattern of the same drug in a perfectly feasible manner (e.g. a immediate releasing drug in incorporated in the outer coat layers. And the sustained slow releasing drug is formulated and prepared and the core tablet. The core tablet keeping in the centre is very critical in the preparation of the compression coated tablets. This can be achieved by preparing good quality granules and reducing the RPM during the coat compression, etc. (B.R Conway 2008).

Recently, the drawback of compression coating, i.e., keeping the core tablet in the centre of the compression-coated tablets and absence of core in the coat, have been overcome by using novel compression tools in one-step press coated tablet by (Ozeki et al., 2004 and Tokudome et al. 2009). A fix dose combination two drugs comprising telmisartan and ramipril and a diuretic such as hydrochlorothiazide was developed in the form of an immediate release multilayer tablet (Kohlrausch, 2005). Further, the application of compression-coating technique was used to protect the acid susceptible drug and probiotic (Chan and Zhang, 2005). Successful gastric acid protection and colonic delivery of probiotic have been designed using the amylose with carboxymethyl compression-coated tablets (Calinescu and Mateescu, 2008).

Similar to the compression coating, multilayer compressed tablets consisting of a drug layer and one or more barriers (compression coats) applied by tableting, have been studied. For this, novel bi-layer rotary tablet compression equipments are use (Conte and Maggi, 1996; Chidambaram et al., 1998; Streubel et al., 2000). These barriers can provide a modified delayed drug release by limiting or reducing the available surface for release of drug and controlling the penetration rate in the medium. The core of an impermeable cup system has been used for delayed drug release. Drug releases after the erosion of the top surface, while impermeable cup prevents the release from the lateral side (Efentakis et al., 2006).

The TIMERx Burst CR from Penwest Pharmaceuticals Co. was formulated as an immediate release of decongestant and plus with 24 h extended release. Drug for the immediate release was incorporated in the coating and the remaining drug was formulated in the matrix to achieve a 24-hour release profile. The matrix consisted of two
polysaccharides, xanthan and locust bean gum. Interactions between these components, they form a tight gel in an aqueous environment with a slowly-eroding core (H. Omidian et al., 2011).

Compression-coated tablets with multiple layers of desirable therapeutic result can be developed. Multiple layer press-coated tablets containing immediate release (outer coat), extended-release (middle coat) and immediate release (core), has been patented by Impax Pharmaceuticals Inc. Different drug release patterns can be obtained by adjusting drug loading and polymer type in each layer (Ting and Hsiao, 2002).