2.2 Review of Literature

➤ **Albert J et al., 2003,** Obesity is the one the most common disorder considered to be prevailing in the American population and the statistics show that more than 60% are overweight or obese. There is also prevalence of depression among the 10% American population. If we consider in a logical manner the existence of depression and overweight (10% and 65% respectively), we can easily understand that there is a lot more probability of co-existing of both this disorders. Many clinical studies carried out on obese persons have delineated the fact that obesity and depression co-exists. The researchers have emphasized that the prevalence of major clinical psychological distress or depression is one of the main cause of obesity. Furthermore, this association leads to disordered eating that could be triggered by the stress, anxiety and depression in obesity. Some very interesting facts have been delineated when treating the obese patient with depression and depressed patient with obesity. Treating one disorder has lead to decrease in the other disorder with a fascinating response in most of the cases.

➤ **Ann-Marie Mongan, 2006,** Obesity is now a chronic epidemic disease with drastic health consequences, which will have an impact on both the psychosocial and physical well-being of an individual. Extreme ratio of BMI is associated to morbidity and mortality. To explain this a J-shaped curve illustration has been used. Various factors seem to be implicating the pathophysiology of obesity among them behavioural, environmental and genetic factors are most important. The present day lifestyles also are contributing to developing children and the adolescents obese. A much emphasis has been given the clinical weight loss management programmes. But the results show that 90% to 95% of the individuals have regained the previous weight. Therefore, it is necessary to put more emphases on addressing the actual underlying mechanisms like environmental, social and cultural factors which also act as a barrier. Therefore,
efforts are to be made to reduce weight and prevent weight gain by addressing the basic factors acting as barriers to the weight loss.

- **Asim Sattwa Mandal, et al., 2010,** Compression coating of tablets like sugar coating function as thick protective layers and also it will cover the very bitter taste of an active pharmaceutical ingredient or cover the improper mottled appearance or even provide a barrier for a drug substance that irritates the GIT. Chronobiology the science dealing with the physiological cycle in the body, has made a great advancement in the recent times. And a totally new concept of chronopharmacology drug delivery approaches has been elevated to new levels. But, the major limitation have been in the design and development of particular DDS that can match the physiological cycle or rhythm still requires the availability and use of the particular technology like Pulsatile drug delivery system.

- **B. Rospond et al., 2015,** According to the latest WHO survey it is estimated that presently in the approximation of 35% of the global population is either overweight or obese. The most popular parameter used for the estimation of the overweight or obesity is the BMI. It is now proven by the various clinical animal and human studies that the cause of the obesity is not only physiological but also psychological considered as the central nervous disease. For this reason, monoamine reuptake inhibitors have been the most commonly used drugs for the treatment of obesity. In the present study also the data coming out from the animal model study proves the fact there is dysfunction of CNS. That cause decrease concentration of serotoninergic (5-HT), dopaminergic and noradrenergic leading excessive food consumption or binging disorder. For this reasons, the research in development of weight reducing or anti-obesity drugs, in the last decade was aimed at enhancing the 5-HT concentrations inside the CNS. Because of this drug like Sibutramine is a 5-HT-NA reuptake inhibitor and also that acts as anorexic agent was approved in Europe and US for the treatment of obesity. The study of human CNS by neuroimaging has confirmed that exposure to palatable food can activate the parts of the brain as those observed during drug craving. Therefore, in some cases, obesity can be considered as food addiction.
multi-phase complex disease and for the management of obesity not only metabolic measures but also psychiatric treatment needs to be considered.

**B.R Conway 2008**, Compression Coated Tablets are the tablets that are coated applying the compression, using a specially designed tablet compression equipments. A method or process of same can be used to prepare the layered tablets having two, three or more layers. Especially, when the physical or chemical incompatibility exists and the physical separation of the active or inactive ingredients is required. And further to produce the repeat action dosage form. The prepared formulation of dosage form can be designed to produce immediate and a sustained release of drugs. The unique technique of compression coating generally has a two to three steps. Preliminary the pre-compression of a relatively soft core tablet is done as an initial stage. Then the first layer coating material granules or powder is placed in the die cavity, on this a precompressed core tablet is placed and a light similar to the precompression a compression is done. Further, the upper or the third covering coat layer granules are added and the final main compression is done with the required hardness to bind together the layers of the tablets. In a similar way, chewable tablets are the one of the popular dosage form that is designed and prepared to be sucked in the mouth and disintegrated prior to swallow. The advantage of the chewable tablets is patient compliance and convenience with probably enhanced bioavailability. The in vitro dissolution testing for chewable tablets is carried out as per the monograph similar to the conventional tablets. Because the patients will chew the tablets and the disintegrated and dispersed particles are swallowed or sometimes the patients will skip the chewing and swallow the whole tablet. Therefore, the dissolution study of the chewable tablets as per the most of the monographs is carried out in the gastric buffers. However, as indicated, these tablets will have excipients either to mask the taste or enhance the palatability. The processing prior to manufacturing will be carried out in a different manner. There are many critical factors in the design and development of chewable formulations. The taste masking evaluations is one of the important parameter in the optimization of the chewable dosage
form. Novel technologies like the electronic tongue is now a days available to evaluatte taste properties.

➢ **Barbara E et al., 2009,** American Psychiatric Association defines the Bing eating disorder as compulsive overeating on a regular basis. It normally occurs as an episode during which a person will consume more food in an hour or two that would usually be consumed in the entire day. Symptoms of bing eating disorder are the lack of control over eating and the person will eat more quickly than usual and feel guilty or disgusted after bing eating. Bing eating is generally triggered by depression, anxiety or other psychological disorder. This condition can do serious harm to body and mind, affecting the internal organs, mood and self-esteem of a person. People suffering from eating disorder are often fat or have excess weight. As the Bing eating disorder affects the psyche and body. The disorder may cause various co-morbid diseases like, elevated cholesterol, Diabetes, Hypertension, Hormonal imbalances, GIT problems, Sleep apnea and Arthritis, etc. Treatment for binge eating disorder involves the use of prescription medications like, SSRI- Fluoxetine Hcl. VNF Hydrochloride (SNRI) and BPN Hydrochloride etc., medications in combination with CBT to control the desire to binge or to reduce the symptoms of a co-occurring mood disorder. Fluoxetine, a SSRI is the only drug given approval for the treatment of Bing eating disorder by FDA. If a particular patient is suffering from depression, anxiety or other psychological disorder, treatment for these conditions must be an integral part of recovery.

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Brandon H. Hidaka et al., 2012, In this review the authors have tried to determine the present status of the depression in the general population all over the world. During the process, the data collected indicate that there is a drastic increase in the depressed population and also the prevalence of depression on several occasions in an individual's lifetime also has increased. But the limitation of this study was a strong conclusion cannot be drawn due to conflicting results and the possible drawbacks in the methodology used. However, there are enough potential explanations available to justify the increase in the depression rate. People in search of modernization have themselves increased the expectations, and falling short of those expectations is the most likely sure culprit for the increase in the depression rates. The country's GDP per capita was found to be correlated with the depression. In the study, it is taken as a quantitative measure of modernization and lifetime prevalence of depression or mood disorder is significance. For a person to be happy well-being are intimately related. In conclusion, the growing stress with higher expectation is leading to depression chronic diseases like obesity that is a basic reason for most of the coexisting or morbid diseases.

Bruno Halpern et al., 2010, have reviewed the possible combinations of medication that have been used clinically in the treatment of obesity. Depression and anxiety disorders along with the eating disorders are the risk factors for the rapid development of obesity. The treatment of the obesity as illnesses along with
the psychological treatment has many times shown fluctuations in the weight, depending on the drug class that is used. ORL with serotonin and noradrenaline reuptake inhibitors (e.g., Fluoxetine and VNF) reduces the slight up to five percent of the weight.

➢ **Burcak, 2011,** Obesity is routinely characterized and diagnosed based on the body mass index ratio. Even though obesity carried various common psychological symptoms found in the eating disorder, but still obesity is not considered as eating disorder. However, generally the physicians and researchers classify the overweight or obese patients into two main subgroups; the obese patient having the binge eating disorder (BED) and those without BED. And also the rate and extent of psychological distress or depression is found in the obese patient with BED. In the previous studies reported the pharma therapeutic treatments prescribed for the treatment of BED are the antidepressants like, Fluoxetine, Sertraline, VNF, Sibutramine and Buproprion etc. In most of the studies, it is emphasized that these antidepressant medicines reduce or stop the BED episodes. In the present case report, it was found that the subject was reluctant in reducing the weight leading to bipolar depression. Therefore Fluoxetine was given along with cognitive behavior therapy, and that was found to be effective in regulating the weight and the symptoms of BED. The patient has also followed the diet and exercise regularly instructed by the physician. Finally from the case report it can be concluded that a proper psychiatric diagnosis and the psychopathological approach is necessary for the treatment of an obese patient with BED.

➢ **Carla M. L et al., 2006,** They worked on compressed mini-tablets as a dual phasic sustained drug delivery system, designed to be releasing the drug in the zero order kinetics. To attain the immediate release, the empty spaces in the voids between the mini-tablets were filled with the immediate releasing formulation. The outside layer was releasing the drug rapidly in a very short time. And the mini-tablets were formulated to provide a prolonged release. Different composition (HPMC or EC) and the number (10 or 21) of mini-tablets were used to obtain different drug release rates. Based on the calculations of the release
kinetic parameters, it can be concluded that mini-tablets containing HPMC (12%) were suitable approaching zero-order (constant) release over eight hr time periods.

- **Carlos et al., 2005**, from the different studies the obesity and binge eating disorder (BED) association was confirmed. It has proved that Cognitive behavioral therapy (CBT) has efficacy for the treatment of BED but not obesity. But till date no studies have been done to evaluate whether adding obesity medication to CBT will help or increase the weight loss. In the present study fifty obese BED patients were selected and provided a four week treatment of either ORL 120mg thrice daily with the CBT or placebo with the CBT and were followed even after the treatment up to three months by the double bind method. The significant of the study was the ORL randomized placebo controlled trial study was conducted along with the guided assistance of CBT. The results demonstrate that the addition of ORL to CBT was providing a greater reduction in the weight than compared to the placebo to CBT. These clinical improvements were observed till three months followup after the discontinuation of the treatment.

- **Christina J et al., 2009**, The authors have tried to assess the intensity of depression related with the symptoms as a disease in the obese children, not only will lead to better strategize the treatment for the primary care provider but also prevent and mange the coexisting obesity and prevent further complications. Particularly the mental disorder as depression and anxiety, the psychological disorder that are once considered to occur only in the adults are now increasingly common in the children. Depression in the children with obesity has shown to have very serious health effects which include different kinds of physical and psychological disorders. And the coexisting pathological ailments could be for a period of short or long term. However, the signs and symptoms that can be seen in the early stage like, reduced or shortened sleep, sedentary lifestyle and depressed mood will suggest the predictor of depression which may overlap predictor of obesity.
Christine et al., 2002, The authors have studied the scenario of a rising obesity epidemic, economic burden in the seven major countries including the US and some European countries. Even though efforts are being made to showcase the drastic health consequences of the increasing weight or obesity, there is no shift in the mindset of the people towards healthier lifestyles. The authors also highlights the modest availability of the weight loss drugs and predicted that in the coming next ten years the potential market for the management of obesity could rise above the US $1.3 billion.

D.H Barich et al., 2005, all the properties of active and non active substances are very important in the development of any pharmaceutical dosage form. In the pharma industry a formulation scientist likes to be associated with the formulation of solid form of the drugs and non active substances. The main reason for this is the stability of both the active and nonactive substances in the solid form in comparison to the liquid form. However the challenge is to make the solid form more solubilize in the GIT so that it can be absorbed easily through the biological membranes. More importantly the determination of the solubility is important as, it can be affected by many factors like, pH, temperature and nature of drug i.e., hydrophilic or hydrophobic. In general during the formulation the scientist will consider more specifically chemical and physical stability.

Davis and Carter 2009, the review article has presented the opinion that the compulsive excessive overeating or binge eating has many similarities to the drug addiction. The proclaimed report is 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. On the other hand, excessive eating is homologous to the other addictions like alcoholics, gambling or shopping as that the activity itself is rewarding and reinforcing. So here we provide some recommendation for the
modification of treatment that recognize the similarities between the drug addiction and the compulsive excessive eating.

- **E.J. Leehr et al., 2015**, In this review of emotion regulation in binge eating disorder and obesity the authors have systemically reviewed the complete literature available in PubMed, PsychInfo and Medline till the end of 2014. In the review the emotional aspects of the obese binge eaters and obese non-binge eaters are investigated to make a clear distinction of the binge eating disorder groups. We have selected only the experimental studies published in the peer-reviewed journals. It is reported that obese patients with BED have a distinct neurobiology that is characterized by deficit in the emotion regulation. But we have focused on the exclusive studies; those have carried out as per the ecological momentary assessment (EMA). From the data obtained roughly it can be hypothesized that impulse could be the possible explanation for the cause of binge eating triggered by the negative emotions. Because of the deficit of the emotion regulation the binge eaters could be unable to control the negative emotion and their high level of impulsivity could lead to binge eating. In the conclusion, we found enough evidence that indicate the increase negative emotion effect often serves as a trigger the binge eating in the obese binge eater unlike in the obese non-binge eaters.

- **F.S. Luppino et al., 2010**, A through systematic through literature survey involving repeated observations of the same variables over last few decades was carried out. This vast literature survey was done using the different scientific search engines like EMBASE, MedLine, PsycINFO and PubMed. Various database published up to March 2008 were collected based on the different criteria. The study examined the two-way relationship between depression and overweight. The results of the study delineated the association between the obesity and depression. Both obese persons and depressive patients have approximately equal chances of inheriting the comorbidity. The finding of this literature survey is that there is a two way association between obesity and depression. These findings will assist the physicians to diagnose the obese person psychologically and monitor the depressive patients for possible weight gain. And
the results are also a alarming caution for the both patients to keep an eye on the developing symptoms carefully.

- **G. Castelnuovo et al., 2013,** Morbidity and mortality can occur from various diseases like, different types of cancers, cardiovascular diseases, diabetes, dyslipidemia, Stroke, musculoskeletal disorders and even psychiatric disorders. But growing excessive body weight is a very important risk factor and it is estimated to cause yearly more than three million deaths worldwide. Comorbidities of obesity that leads to disability are the actual socio-economic burden of obesity globally. Etiology of obesity is difficult to understand and explain as it is a multifactorial. One assumption is the genetic cause with the environmental and behavioral factors that leads to the different conditions like increase in the adipose tissue and over expression of some hormones like ghrelin. There is important delineating factor came out of this study that the effects of chronic psychological disorder may lead to a condition of obesity in the excessive eater. The existing stress and the easy availability of quality foods lead to bing eating and obesity. Presently the focus is on discovering the temporal and causal relationship between psychological distress and obesity. Obese individuals have been strongly stigmatized and they have to cope daily with growing modalities of discrimination and prejudice about the overweight. The significant psychological consequences of the weight discriminations are well reported. Various clinical researches have proved the fact that bing eating disorder in more common in obese individuals. Clinical Psychology has to face the global obesity challenge, providing more evidence-based protocols for the psychological rehabilitation in obesity both in the traditional and new remote clinical settings.

- **G. T. Wilson et al., 1992,** The prevalence of bing eating among the obese patients is thought to be between 20-40%. This subgroup of obese bing eaters differs from the obese non bing eaters in many ways. Obese bing 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 bing eaters also have significantly greater psychological distress, especially depression. They always think about
palatable food worry about their weight gain than the nonbing eaters. Finally, the obese binge eaters show a isolation characteristic such as secretly eating and are cautioned about being caught in the public. In our present study the results have shown that approximately two third of the subjects reported of bing eating prior to becoming fat. And the remaining obese subjects have developed bing eating disorder after becoming fat.

G. Z. Zhang and D. Zhou 2009, The maximum numbers of the pharmaceutical products manufactured currently are solid dosage forms. In pharmaceutical industry solids are categorized into mainly; amorphous, liquid crystalline and solid crystalline are the three forms. 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. Depending on the nature of the physical state of the components attached or trapped in the crystalline lattice of a crystal it could be a hydrete, salvate and co-crystal. If the substance is water it is called as hydrate and if any solvent is trapped, then that crystal is called as solvate. Cocrystals are the novel class of crystalline solids; which are made of neutral molecules at ambient conditions. The melted solid crystal will turn into an amorphous at room temperature below its melting point. This transition of crystalline substance upon heating beyond its melting point to an amorphous substance is called the transition temperature of glass (Tg). Most of the active pharmaceutical ingredients used in the pharmaceutical formulation are the salts, polymorphs or amorphous in nature. Cocrystals an intentionally produced crystalline product combining two neutral solids, has yet to be explored in pharmaceutical products. Moisture uptake by the solid substance can greatly impact the solid forms. For example, if a metastable solid comes in contact to water a suspension is formed then conversion to a stable phase is mediated through the solution mediated phase transformation. Polymers are the very high molecular weight substances and can be used as carriers including other additives to cover or coat the particles and avoid the transformations of polymorphs from one form to another form.
George A. Bray, 2013, In this review article the author emphasis the necessity of the various medications for the treatment of obesity. Because they enhance the weight loss process induced by the behavioral, physical activity or diet control. New medications that are under the process of trials are also required to be approved. Because a minimum weight loss of even five percent or more will significantly reduce the various health risks in obese individuals. Especially the chronic diseases associated with cardiovascular, liver cirrhosis and diabetes. Furthermore, a slight more reduction in weight in the range of 10-15% on an average, achieved by surgery can reduce the mortality rate. The medication used to treat the obesity goal is to assist the patients in reducing the weight loss. The author, therefore, discusses the currently available drugs for obesity management.

George et al., 2000, In this review article the author discussed the different types of the drugs used to treat obesity. The medication presently used to treat obesity can be classified into three categories like, the drugs that increase thermogenesis like caffeine, selenium, ephedrine and different herbs, that can be used in singularly or combination. Second category is of those drugs that alter metabolism like ORL is an enzyme lipatic inhibitor that can avoid the fats taken in the food being absorbed. The third category is of those drugs that reduce food intake like (5-HT), dopaminergic and noradrenergic blockers and mazindol. There are also some high molecular peptides that affect the apetite, but are still in the process of development. The combination of caffeine and ephedrine which enhance the thermogenesis was tested in the clinical trials, but failed to get the approval by the regulatory agencies. However, there are many drugs that are under trials being investigated to get the approval.

Gerold Mosher et al., 2007, Complexation of drug is one of the many strategies to effectively enhance the physicochemical properties of pharmaceutical compounds. Cyclodextrins are classic examples of compounds that form inclusion complexes. These complexes are formed when a drug substance is partially or fully incorporated inside a host molecule, e.g., cyclodextrins with weak bonding. When the inclusion complexes are formed, the physicochemical parameters of the guest drug substance changed or altered and improvements in the drug substance

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solubility, stability, taste, safety, bioavailability, etc., are commonly seen. The safety of orally administered β-CD has been investigated in numerous studies with extensive evaluation of hematology, blood chemistry, urinalysis, and necropsy (macro and microscopic). There was no toxic effect observed in any of these studies after oral administration of β-CD to mice, rats, or dogs.

- **Banker and CT Rhodes, 2002**, in their book Modern pharmaceutics, chapter ten, discussed the importance of the tablet dosage forms and the components required in the preparation of tablets. They described the different methods of processing of tablets and also discussed about different types of tablets like Chewable tablets, buccal tablets, sublingual tablets, fast dispersible tablets and the modified release tablets like, delayed release tablets etc.

- **Goossens L, et al., 2009**, The study found that the lack of control (LC) during eating in the fat children and adolescents. Recent studies have proven a association between the lack of control over eating and the emotions and this experience is significant in relation to the symptoms of anxiety and depression in obese individuals taking treatments for weight reduction. The results have demonstrated that the presence of depression and anxiety along with negative emotion is significantly linked with an emotional eating or bing eating. More importantly anxiety was found to be associated with the lack of control during eating. It was found that the very fat patients taking treatment are more prone to lack of control during eating due to anxiety. These patients can be benefitted if the physicians concentrate on both reducing the weight and also the psychology of the patients. Finally, it can be said that the overweight patients who are having the symptoms of physiological distress use the bing eating to cope the their negative emotions.

- **Haddock et al., 2002**, This study was planned to conduct the RCT to evaluate the affect of antiobesity medication both singularly and in combination. The RCT was conducted under the stringent guidelines with the total of more than hindered studies were carried out and are reported in the database. These huge clinical trials had compared antiobesity medication of single and combination drugs to dummy and comparisons of medications to one another. The results delineate that all the
drugs have shown average effect. However, four drugs have produced greater effect viz., Sibutramine, amphetamine, benzphetamine and fenfluramine. With and without the dummy or placebo effect, the weight loss for a single or combination drugs was not found to exceed four kilograms.

- **Han van de et al., 2003**, In the absorption or penetration of the drug through the biological membrane the most important properties to be considered are the dissolution and solubility. In the process of absorption the biological membrane is considered as the both physicochemical and biological barrier to the penetration of the drugs. Therefore before a drug can be absorbed through the membrane it must first get dissolved and should be present in solution form for being absorbed through the biological membrane. Hence in case of the BCS class II and IV drugs solubility of drugs will be the absorption rate limiting factor. Therefore solubility is now seen as a property to be addressed during the early stages of drug discovery or early stages of drug design. Increased lipophilicity is a common cause of poor solubility, that can lead to reduce and incomplete absorption following oral administration. Octanol/water partition log P and distribution log D coefficients are the parameters that are widely used to make the determination of drug absorption through membrane penetration and permeability. This includes the gastrointestinal absorption, blood brain barrier penetration and correlations to the pharmacokinetic profile. Several approaches for higher-throughput lipophilicity measurements have been developed in the pharmaceutical industry, including automated shake-plate methods, and some of these are now available commercially.

- **Herbert A Liberman et al., 1990**, Layered tablet are one of the fast growing dosage forms, which are composed of two or three layers of granulation compressed together as a single layered tablet. They have the resemblance appearance of a sandwich. The layered tablet dosage form has the benefit of keeping the two incompatible substances separately with an inert barrier between them. With the layered tablets, a combination of immediate and sustained release drug release can be produced from a single tablet. In the some earlier works of
three layer tablets, a sustained release layer was sandwiched between the two immediate release layers.

- **I. Stoltenberg et al., 2011**, have developed orally rapid disintegrating mini-tablets as an effective and compliance dosage form for paediatric patients. By using the five ready-to-use, commercially available tableting excipients, Ludiflash, Pearlitol Flash, Parteck ODT, Prosolv ODT and Pharmaburst 500 as directly compressed into minitablets, with 2 mm in diameter, were examined. Fast or rapid disintegrating minitablets have the dual advantage of both solid dosage form of stability and liquid dosage form of ease of administration with added advantage of reduced cost. In the present study the formulation containing the ludiflash of rapid disintegrating minitablets are shown to have produce rapid release of the drug with good compaction and stable enough to withstand the attrition during the transportation.

- **Ioan Tomuta et al., 2007**, have investigated have studied the sustained release coated mini-tablets of Metoprolol Tartrate drug release kinetics applying the complete experimental factorial design taking two factors and three levels. The mini-tablets were prepared by the most common method wet granulation using five millimeter punches and were coated with an insoluble polymeric film (Eugragit grade). They found that eudragit polymer of particular grade has the most important influence on the drug release percentage at different intervals of time.

- **JA Linde et al., 2004**, The objective of the study was to find a relationship between obesity, depression and bing eting among the fat patients seeking weight loss treatment. Bing eting is characterized as overeating episodes a feeling of unable to control, followed by guilt feeling and attempts to reduce eating to loose the weight. The prevalence of these behaviors is estimated to be high as forty to fifty percent in individuals who are on the prescribed treatment for obesity. The uniqueness of the study was its ability to find the psychosocial aspects of obesity in a large population. The scale that was used in this study (depression, binge eating, medication status, weight control self-efficacy). The study has delineated that negative emotions were highly present among obese who are on the
prescribed medication and poor outcomes were the results of medication. The findings have confirmed a high prevalence rates up to the lifetime of depression and binge eating as common co-morbidity in individuals with obesity. The study raises many questions like, whether the presently available obesity treatment guidelines sufficiently address the requirement treating the obese individuals who have co morbid symptoms of binge eating and those who are also taking medication for depression.

➢ **K. H.Ba and M Zahn 2009**, Stability is a critical quality attribute; therefore, the stability program plays an important role when developing new pharmaceutical products. The new dosage form stability protocol should follow the guidance from the parent stability guideline principle. The ICH process was able to harmonize the expectations and requirements in the three regions: European Union, United States, and Japan. The stability study was carried out as per the international guidelines and the stability data obtained confirm the drug product quality by assuring that the drug product continues to meet its specification throughout its shelf-life in the region that it is registered. The storage conditions impacting the drug product are determined as a combination of light, temperature, and humidity. For a drug product stored at room temperature, the guideline defines an intermediate condition of 30°C/65%RH. Testing at this intermediate condition is needed only when a significant change occurs for samples stored during six months under the accelerated condition of 40°C/75%RH. If six-month data at accelerated condition do not meet room temperature specifications, samples at intermediate condition stored to twelve months will be tested. These data will be submitted in the NDA.

➢ **Donnell and Williams 2012**, Complete knowledge of active pharmaceutical ingredients during the preformulation studies is very crucial especially for poorly water-soluble drugs. As it is estimated, seventy percent of the drugs are poorly water soluble and belongs to the BCS class-II system. The experimental method for determination of solubility is by direct determination by placing the excess amount of solid in aqueous solution. In this method, the suspension kept at constant temperature is shaking for two days. Then filtrate sample is withdrawn at
regular interval to analyze the drug content by suitable analytical method. Solid form characterization of active pharmaceutical ingredients provides valuable information necessary for the formulation development. The existence of drug in a particular solid form or transformation during the processing could completely change the physicochemical characteristics or the API. Drug and excipients compatibility study is carried out also during the preformulation of the physical blend of the components, and a processed sample of the components. Gentle blending of the powders in the desired ratio in a mortar with a spatula at ambient temperatures is recommended. The processed sample may be as simple as a co-ground mixture or may be a final formulation such as a tablet or capsule dosage form. Fourier transform infrared spectroscopy is most widely used methodology to study the drug and excipients interactions. Powder particle size and shape analysis by coulter counter and scanning electron microscope is preferred method. Finally the solvent remained especially the organic solvent determination is important with respect to safety of any dosage form. For this purpose the headspace gas chromatographic analysis is preferred.

➢ Kakkar and Dahiya 2015, Obesity is presently a rapidly growing epidemic disease that is a serious concern for the healthcare system, as it is causing huge economic and psychosocial consequences. Worldwide obesity ranks as the fifth common risk factor for the deaths. In the present scenario, there should have been many pharmacotherapies for the treatment of obesity. But due to various limitations and adverse effects many anti-obesity drugs have failed approval in the clinical phase and some of the approved drugs by FDA have been withdrawn due to various adverse effects seen post marketing phase. Currently, only four drug products are approved by FDA for the weight management or treatment of obesity in adults; ORL, phentermine-topiramate, lorcaserin and naltrexone-BPN. Among this four drug products only ORL is approved for management of obesity for a longer period and as 60mg dose ORL in now available over the counter drug. As many pharmacological options in obesity treatment are being evaluated and some seem to be emerging, like the FDA's recent approval of naltrexone-BPN combination therapy for the obesity. However, obesity currently is one of the
most common causes of mortality, and, like other chronic diseases sustained efficacy proven weight reducing pharmacotherapies including multiple or polytherapy short and long term treatment strategies should be explored.

Kendall and A. W. Basit 2006, Solid oral dosage forms can be divided into two main categories: immediate release dosage forms, where disintegration and subsequent drug release and dissolution occur in the stomach. And the modified-release technologies, which utilize polymers to alter the site or time of drug release within the gastrointestinal tract. The use of polymers as excipients especially in the conventional immediate-release dosage forms is commendable. Polymers have been used either as an aid in the formulation and manufacturing process or to prevent drug from degradation upon storage. The judicious selecting of excipients is very important to enhance the in vivo efficacy of the dosage form. Disintegration and subsequent drug release and dissolution and, therefore, absorption and bioavailability (i.e., pharmacokinetics) to some extent can be controlled by the choice of excipients. Capsules are used as an alternate solid dosage form to the tablets. Most of the excipients that are used as diluents or disintegrants are same as used in the conventional immediate release tablets. Hydroxyl propyl methyl cellulose is a versatile polymer used in oral and topical formulations available in different grades and. A less viscous two to six percent of HPMC can be used as a binder in all the three tableting processes viz. wet granulation, dry and direct compression tableting processes, as well as for film-coating of the compressed tablets. At slight higher concentrations up to 35% Hpmc grades can also be used to prepare sustained or extended release dosage form. The water-insoluble polymers that are routinely used for extended-release applications are the various types of cellulose derivatives like, methylcellulose, ethylcellulose and cellulose acetate phthalate, amino methacrylate copolymers like, Eudragit RL and RS-100. These two polymers have a difference in the quantity and arrangement of quaternary ammonium compounds making Eudragit RS more hydrophobic. Likewise, other hydrophobic polymer ethylcellulose is available in different grades with varying viscosity. Ultimately, how this complex
drug delivery system prepared using drug and polymers, releases the drug for absorption in the gastrointestinal tract is of prime importance.

- **L. Bekker et al., 2014**, Bing eating is an eating disorder afflicting more than six percent of the American population. Binge eating is an intermittent excessive consumption of food in a small gap of time. BE has shown a strong comorbidity with the overweight and obesity along with other disorders. In the various study, it is proven that more than half of the Bing eaters are either overweight or obese. The crucial facts related to binge eating such as obesity, adolescents as an age group was the objective of the study. In the study obese OLETF rats were used. In the study, it was found that the adolescent rats were rather more prone to binge eating. Compared to adult rats the adolescent rats showed eagerness and increase in ensure intake. Therefore, the findings of the study suggest that the adolescent rats especially the obese adolescents are at more risk for binge eating and this binge eating can lead to obesity. In the study resemblance to the real life situation similar with binge eating in humans was employed as DSM-V recommended criteria for the study. Thus, the study concludes that the adolescents and in particular obese animals are more prone to developing binge eating disorder. And, recommends the further examining of biological mechanisms considering the factors like obesity and age for developing the binge eating disorder.

- **L.M. Gianini et al., 2013**, The study examine the relationship between the emotional overeating and the eating pathology in sample of obese bing eater adults. It was found during the literature survey that substantial literatures indicate that obese individuals with bing eting disorder reported having overeating or bing eating in response to the emotions. Many clinical trials have examined the efficacy of treating the obese bing eating disordr by employing the emotion regulation skills, so that the negative emotional overeating can be controlled. In our study, the results indicate that when an obese individual with BED feels the high levels of negative emotions, they will lack the effective strategies for controlling or managing these emotions. From the results, the mean negative effect of emotions was comparably same with a moderate level of depression. For this reason, it is possible that overeating or excessive eating is undertaken as to
mange and regulates the negative emotions. Therefore, we recommend that the future studies should try to find the impact of negative emotions on overeating or binge eating disorder. And also the studies should compare the effectiveness of the combination of treatment for the obese patients with binge eating disorder.

- **Leonore de Wit et al., 2010**, From the vast literature available now it is crystal clear that there is an association between depression and obesity in the people suffering from either obesity or depression. Many studies have gathered strong evidence for occurrence of obesity for the coexisting of depression. However many questions are still unanswered. One of the important queries was how the intensity of the depression or severity of the excess weight influences this association. Therefore in this clinical study it was found that decrease in the weight of obese patient reduces the depression and reduction of psychological distress or depression will also reduce the weight in the obese patient.

- **Licinio J and Wong M 2003**, Obesity is a heterogeneous disease the cause could be genetic, metabolic, economical, social, environmental and psychological. Compared to the other psychiatric diseases depression and anxiety are seen more commonly in the obese individuals compared to the non-obese individuals. Obesity and depression are the rapidly growing major health concerns of the public today. It is proved by various studies that some of the brain parts afflicted with depression also get disturbed in case of obesity. These two disorders are often seen overlapping at multiple levels. In addition drugs used in the treatments of both disorders in most cases will act through the same neurotransmitter systems 5HTs, serotonin and norepinephrine reuptake inhibition. Mood swings or psychological distress could be the adverse effect of the obesity treatment drugs and changes in the weight could be the adverse effect of the antidepressant treatments.

- **Longena Ng et al., 2013**, The authors have studied the carving for food in binge eating disorder. The study has findings that the level of cravings for food may be sufficient to predict overeating in BED. And that treatment should target this as defining features that will differentiate the patients with BED from those who do not binge eat. Normal-weight and overweight controls were used in the study to
ensure that the findings were specifically underlying the eating pathology. This study showed that the food craving is correlated to over-eating in BED and that this is not a result of hunger or calorie deprivation. One of the main contributing factors to the rising obesity rates is compulsive overeating a peculiar symptom of BED.

- **Louis et al., 1998**, 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.

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

- **M J Devlin, 2001**, Treatment of the obese patient with the binging disorder is a real challenge. Because the physician has many tasks to handle the single patient like, first stopping or at least controlling the food carvings or binge eating habits. Second, improving the physical health or reducing the weight. Third, making the patient feel better or treating the depression that has occurred as comorbidity in an obese patient with BED. Many psychological and pharmacological treatment approaches need to be used in such patients. Whatever the short term or long term approach the ultimate goal should be to reduce the weight and control the binge
eating disorder. This can be achieved by a combination approach of psychopharmacological treatments along with the beneficial lifestyle changes.

- **M. Jimidar and M De Smet 2007**, The HPLC method development process starts with a thorough planning step in which a development plan is generated based on the method requirement definition, available information gathering, and resource planning. The prerequisites for the smooth development of the HPLC method are, all critical intermediates and starting materials are defined for a drug substance method. Formulation and dosage form compositions are locked for a drug product method. Impurities relevant to the degradation products are known and available as certified standards. Certified standard of the main compound and a selectivity batch or selectivity samples are available. Late phase product specifications are set in the draft. Method development samples (appropriate drug substance batches, formulations and stability samples are available. The following information could be useful like, UV spectra, solubility, pKa, stability of API, and model compounds early characterizing drug product and drug substance. Method development history, late phase formulation composition, late phase synthetic route. Stability and safety data of drug substance and drug product, excipients compatibility data information in regulatory files, etc. are important for clinical trial applications. Review of existing literature and current compliance guidelines and procedures. Method development is a process in which both the development lab and the receiving lab have to work closely in order to generate a test method that is well documented, easily understood, and simply performed by an appropriately trained analyst. Within QC environment, it is not important to have the scientifically fanciest method; a technically straightforward, easy-to-use and most robust and GMP-compliant method is preferred.

- **Malhotra S, et al., 2002**, a randomized controlled trial was conducted to examine the tolerability and effectiveness of VNF hydrochloride in the treatment of binge eating disorder. The study was conducted by choosing the thirty five obese patients with binge eating disorder and taking their consent for the study, at the Cincinnati University where, a program of weight management was conducted. Then twenty nine patients equivalent to eighty three percent were given VNF as monotherapy
and remaining six patients equivalent to seventeen percent were given as adjunct therapy for the six months. The results demonstrated that VNF was effective in controlling the severity of bing eating and mood disorder with minimal adverse effects like, dry mouth, nausea, decreased libido and insomnia. A slow, steady hypertension was seen in six patients (17%) were of less significance. In conclusion, VNF was found to be an effective and tolerable for the treatment of bing eating disorder in the obese patients.

Marina Marcus et al., 2002, WHO presented a data of estimated people affected by the depression and also put forward the possible reasons. In 2002 in the world, the depression was affecting 350 million people all over the world. Depression is a mental disorder commonly that has the some common symptoms of lack of interest in life like, depressed mood, no pleasure, feeling of guilt, decreased energy, low esteem, improper sleep and appetite with less concentration etc. Depression often comes along with the symptoms of anxiety. The severity of the symptoms of the depression varies from mild, moderate to severe. However, 60-80% of the depression in the world can be treated with the psychotherapy and medication.

M D. Marcus et al., 2009, The study reviews the literature of the past ten years and to examine whether obesity is a mental disorder. Obesity combined with disordered eating was found to be the main culprit in developing the sever obesity and depression. The lack of energy expenditure or reduce physical activity is a lesser cause to rise in the obesity. Among the large percentage of obese individuals a potential contributor for obesity was the psychosocial impairment leading to disordered eating. The studies have reveled that the obese individuals will have weight-related stigmatization in different settings and lead a poor quality of life. In relation to psychiatric morbidity, an association has been found between the obesity and the mental disorders like anxiety, depression and eating disorder especially the binge eating disorder. Even though little evidence from the literature supports to classify the epidemic obesity as a psychological disorder but, there is enough reason to consider excessive accumulation of mass and fat or obesity in the management of depression.
The presence of binge eating disorder is an important indication of comorbid psychological problem especially depression, anxiety disorders, and substance abuse disorders. Binge eating or loss of control eating may be observed in children and adolescents as well, usually associated with overweight or obesity. Two other patterns of disordered eating are frequently associated with obesity: the so-called night eating syndrome and emotional eating. Often anxiety and depression are found to coexist with the binge eating disorder. In the clinical studies it is found that depression at the baseline is associated with increasing obesity in normal women at the follow up period. Likewise, obese women at baseline have a slightly high risk of depression at the follow up period. It is apparent that most of the patients diagnosed with the psychological disorder are prone to get overweight or obesity. People with serious mental disorders like, schizophrenia, CAD, and other psychological disorders are up to three times more prone to have obesity compared to the general population. In one study it was found that obesity and psychological disorder accounts for significant socio-economic burden globally due to internal stigmatization, discrimination and social prejudice. When all these factors are magnified and seen, finally it can be said that there is a multifaceted relationship between the obesity and the psychopathology. Therefore, assessment and treatment of obese patients with binge eating disorder should consider cognitive behavioral as well as pharmacological treatment options focused for treating obesity but also mental or psychological disorders.

McElroy SL et al., 2002, Have performed a vast literature search for the years 1966-2003 and found that there a pathophysiologic relationship between obesity and psychological disorders, that will have implication for the treatment of both conditions. Obesity and psychological or mood disorder share several important common features, particularly erratic eating behavior, appetite, and less activity. The numerous clinical and community studies conducted on the obesity have consistently described disordered excessive eating with increase appetite and physical activity. Psychological distress was found increased in the hundreds of obese individuals compared to the normal weight persons. And also studies have shown that a large portion of persons with depression has increased appetite,
overeating, reduced physical activity, and weight gain so called the atypical features of depression. Binge eating and mood disorder is comorbidity of obesity and found to co-occur. The secondary comorbid diseases develop very slowly with one or more symptoms having effect on all aspect of life. And it is necessary to recognize the comorbid diseases pathology occurring simultaneously in many organs of the body. For this reason from the clinical prospective, it is important to diagnose early by investigation or evaluation the patients and enquire about the symptoms. It is a fact that a clear relationship exists between obesity and cardiovascular diseases. Additionally the psychological problems like depression and binge eating disorder are commonly seen amongst the overweight and obese individuals. Like the CVS diseases, it is proven that minor or major depression in more than fifty percent of obese individuals is seen. Therefore the obese patient examination of both the BMI and waist cutoffs and screening of comorbid diseases is very crucial in the follow up for the management of obesity and its comorbidities.

➤ **Pascale Isnard et al., 2002,** The study was conducted to examine the relationship between the excessively obese adolescents who are on the prescribed treatment and psychopathology related to the bing eating. They found that most of the obese adolescents have increased bing eating symptoms and mental distress. A strong relationship between severity of bing eating and the increased level of depression and anxiety with low self-esteem was found. The authors confirmed that the bing eating symptoms can come early in 20% of the adolescents who are obese. In the study obese adolescent before taking the weight reducing treatment shown the high levels of anxiety and depression with more bing eating symptoms. The results suggest that obese adolescents with severe bing eating disordr having higher level of mental distress require other forms of treatment. In conclusion, in the obese adolescents an assessment of bing eating and comorbid psychopathology is necessary and psychological support must be provided during the course of medication treatment.

➤ **Peter Davies 2009,** for medication drug delivery, the oral route of administration is the preferred route and is therefore widely used method. In the oral dosage
forms tablets and capsules are the most preferred and widely used solid dosage forms. Therefore the manufacturing or the formulation scientist should have information about the information of basic physical and chemical properties of both the active non-active ingredients used. Like the particle shape and size distribution that will assist in knowing the flow characteristics of the powders. Apart from the powder flow properties mixing is crucial in the preparing of the all solid dosage forms. Further the active pharmaceutical ingredient and the excipients stability is crucial in the development of the solid dosage form. Once the preliminary studies are over in the formulation the type of excipients used and the amount or quantity they are used are of most important. Further the method of processing of tablets and capsules will ultimately leads to the development of the quality solid dosage forms. Because each method has its own advantage and drawbacks.

➤ Philip Rowe 2007, Normal ranges are frequently based on the mean ±2 SDs. With a low SD, the data are all clustered tightly around the mean and the distribution is tall and thin. With more scattered data (higher SD), the distribution is low and wide. Many statistical routines are liable to produce misleading results if applied to data that depart severely from a normal distribution. It is recommended that a check for gross non-normality should be made by producing a histogram of the data and checking that the distribution is unimodal, symmetrical and free from sharp cut-offs at either high or low values. Data that are not symmetrical are described as ‘skewed’. In positive skew, there are outlying extreme values, all (or most) of which are above the mean. In negative skew, the outliers are below the mean. The ‘normal range’ for the value is frequently equated with the range mean±2SD. This is pragmatically useful, but the 5 per cent of values outside this range can be overly simplistically interpreted as evidence that the individuals concerned are ‘abnormal’. Scientific data consist of randomly selected samples from larger populations. The sample is used to estimate the mean of the population. The use of standard error of the mean is to indicate the extent of random sampling error that would typically arise with a particular sampling scheme. It can be calculated by taking account of the sample
size and the SD. The technical definition of the SEM is that it is the SD that would be found among a hypothetical long series of sample means drawn from the relevant population. The to determine whether two samples have produced convincingly different mean values or whether the difference is small enough to be explained away as random sampling error, two-sample t-test is used. The data in each sample are assumed to be from populations that followed normal distributions and had equal SDs. A null hypothesis is created so that there is no real experimental effect and that for large samples; the mean value of the endpoint is exactly the same for both treatments. According to this hypothesis, random sampling error is responsible for any apparent difference and with extended sampling the apparent difference would eventually evaporate. The P value is used as a measure of the strength of the evidence. The lower the P value, it is less likely that such results would arise by sheer chance and so the stronger the evidence. If we fail to detect a difference that truly is present, this constitutes a false negative or type II error. The interpretation of statistical significance must involve not only looking at the P value for the current experiment, but also taking stock of the previously available evidence as to whether two treatments are likely to give differing outcomes. The paired t-test offers the greatest advantage over the two-sample t-test when values are much higher in particular people than in others, but all individuals show roughly the same change. In such cases, the two-sample test would be degraded by the extreme variation between individuals, but the paired test would only have to cope with the lesser variation among the individual changes. A one-way analysis of variance is used where there is a single factor that will be set to three or more levels. It is not appropriate to analyze such data by repeated t-tests as this will raise the risk of false positives above the acceptable level of 5 per cent. If the ANOVA produces a significant result, this only tells us that at least one level produces a different result from one of the others. While t-tests are used with the simplest experimental designs, a single experimental factor that has just two levels – for more complex designs, analysis of variance (ANOVA) is used.
Pokrajac-Bulian et al., 2013, The study investigates the link between anxiety, depression, and binge eating in the clinical study consisting of male obese adult also having comorbid CVS disease. The study was carried out for approximately one year period, during that period psychological and pathological changes in relation to changes in the weight were observed. In the previous studies it was found that obese patients who pass through some serious emotions like anger, anxiety and sadness try to cope by binge eating. This temporarily provides the pleasure releasing the chemicals in the brain and masks the actual life problems. In The results also we find it necessary to mainly focus on the binge eating disorder as part of weight reduction management strategy. Because treating the psychological disorders will not only be helpful in controlling the weight but also reduce other health risk factors in the obese cardiovascular patients.

R. Dalle Grave et al., 2010, A subgroup of obese patients are proven to show psychological distress and binge eating disorder. Here, we conducted a multicentre study that comprises approximately two thousand obese patients in one of the biggest European medical centre. This project was to evaluate the effect of weight loss on the psychological distress and excessive eating (binge eating disorder). After drop outs due to various reasons, the five hundred subjects remained in the continuous treatment for complete one year. The results conclude that, the successful control of excess weight in obese patients indirectly addressing the psychological distress has showed a delineating improvement in both binge eating disorder and psychological distress. There was a linear relationship between the extent of weight loss and the reduction of psychological distress and binge eating. We recommend future studies must investigate the the combination treatment to maintain the weight loss in the obese patients with BED and suffering from the psychological distress.

Renu Kotwal, et al., 2004, Bing eating disordr (BED) patients often seeks treatment for obesity instead of BED. In this article, the authors present the medication options for the treatment of complicated and uncomplicated Bing eating disorder (BED). It is found that the BED patients are more distressed by their weight that has caused them depression or anxiety. The overweight or obese
patients with BED are routinely present in our center for treatment. The recommended treatment that can be given to such patients includes but not limited to include antidepressants, appetite suppressants, and anticonvulsants. Antidepressants are most widely used for the treatment of BED because of it often association with the mood disorders. Fluoxetine of SSRI class is the common antidepressant used for all eating disorders. Apart from that VNF a SNRI and BPN are next widely used medication for the treatment of BED patients particularly those with obesity. Furthermore, a multiple drug therapy consisting of a combination of ORL with SSRI or VNF or BPN or with some anti-convulsants like topiramate or zonisamide can be used to treat the obese BED patients. The multiple or combination therapy is recommended when a single component mediation trail fails.

Roland Rosmond, 2004, the author has argued strongly the association between the Obesity and depression and the many common symptoms that are in common. The researching author is of the opinion that the Obesity and depression from the literature seem to have taken two separate paths in the treatment pattern. But, form the numerous clinical data and the available literature, huge evidence suggests that obesity and depression could represent different symptoms of a one particular disease process. Obesity and depression could in fact, represent different symptoms of the same disease process. Significantly, obesity is the clinical manifestation of a chronic depression similar to that of major depression. Enough evidence delineates the fact that very intense association is found between the pathophysiology, epidemiology and even in the therapy of obesity and depression. In obesity a gradual increase in the weight makes imbalance in the monoaminergic and neurotransmitters. So, it decreases the serotonin concentration in the central nervous system leading to depression. In such serotonin lacking patients, treatment with the drugs that increases the concentration of serotonin would be beneficial. Therefore, interdisciplinary research is required to identify the common ground shared by these two diseases with a common pathophysiology, assisting in the development of effective treatments.
S. Castrogiovanni et al., 2009, we conducted psychiatric disorder study in fifty overweight patients with Bipolar disorder (BP) and examined the presence of binge eating pattern. The results have showed that many excessive obese patients with bipolar disorder had a lifetime history of binge eating disorder. When we tried to recognise the reason, it was the lack of physical activity and erratic eating pattern during the depressive bipolar episode. There was no major difference between the gender. From the results of the study, we suggest that obese individuals with BD have a high prevalence of binge eating pattern. Therefore, the physicians should be aware and consider this fact while treating the obese patient with BD. And the binge eating seems to cause or aggravate the abdominal obesity accompanied by many medical risks.

S.K. Sing and V. Naini 2007, Apart from alterations in the pharmacodynamics (PD) and pharmacokinetics (PK), the geriatric population suffers from a number of chronic conditions and physical limitations. Clinical monitoring becomes very important to titer dosing accurately. Most of their PK and PD processes take a down turn. Absorption is slower from the oral cavity. In general, the aged skin is more permeable to water and other chemicals. However, the clearance to the blood stream is lowered thus distribution may not be complete. Physically, impairment or decline in vision may hinder one's ability for self-medication. Also, swallowing and chewing may be a problem in elderly patients. Similarly, elderly patients who are edentulous (i.e., toothless) are incapable of chewing any tablet dosage form. Emerging technology has focused on newer dosage forms like the use of quick or rapid dissolving technology (RDTs), wherein, the dosage form quickly dissolves in the mouth and rapid absorption of the drug can occur systemically from the mouth. Furthermore, compliance in elderly patients has also resulted in the availability of sugar and sodium-free products that are beneficial for such age group.

McElroy S.L. et al., 2013, Depression Bipolar disorder (BP) is associated with obesity and binge eating disorder. In the several clinical studies, it is proven that all the three conditions are associated with medical and psychiatric comorbidity. Now it is a fact that the both Obesity and binge eating disorder are associated with
the more psychiatric burden compared to the medical dysfunction in the Bipolar disorder patients. So, in our study we hypothesize bipolar disorder in Obesity with comorbid bing eating disordr could be depended on the body weight. We investigated the, more than seven hundred patients were selected in the psychiatric departments of the group of MayoClinics and a well structured diagnostic questionnaires and interview in the obese individuals of particular demographic population. The findings of the study confirm the relationship between the bing eating disorder and Obesity in patients with BP and also provide more evidence that Obesity and bing eating disordrer are associated with the greater burden of illness in the dpressive bipolar patients. In conclusion, the finding of the study has proved that obese individuals with bing eating disorder seem to have more psychological distress or BP compared to the fat individuals without bing eting disordr.

Scholtz, and Morgan et al., 2009, the study highlight that, if immediate action is not taken more than 50% of adults in UK will be obese by 2050. The obesity with nearly one billion adults overweight worldwide has become an epidemic. Especially in the developed countries over consumption of food with idle lifestyle has led to a vast proportion of obesity with enormous health problems, most of them resulting from psychological disturbance. The occurrence of anxiety and mood disorders is 25-30% higher in obese persons compared to the normal individuals. In obese patients, Psychiatric co-morbidity is related to increasing in the BMI. Obese individuals have a huge stigma and often suffer from depression, anxiety and binge eating disorder. There is recognition that psychological factors, particularly the stress factor are an important culprit in the development of obesity. Bing eting disorder is identified by eating fast in a very short time huge quantity of food with a sense of lack of control. The occurrence of bing eating disorder in the Obese population is almost 30% more than compared to the general population. Not only the BED is affecting the weight loss methods but has been unsuccessful in controlling this epidemic. Therefore, the psychiatric treatment should be a necessary component of obesity treatment.
Seong H J et al., 2010, The major issue of incorporating a drug into fast or rapid disintegrating tablet (RDT) is the taste and the drug needs to have no or acceptable taste for the patients. Otherwise, taste masking should be utilized. Moreover, the drug needs to have good stability in saliva (mainly stable at the saliva pH and aqueous environment) and good permeability. The RDT and also the RDTs should have low or no sensitivity to moisture, but many water-soluble excipients are utilized to enhance rapid dissolving/disintegrating properties as well as to create good mouth feel. In that case some of the aqueous soluble excipients could attract moisture and may destabilize the water-sensitive ingredients. Taste masking is the most integral part in the formulation and the preparation of the RDTs. Different methods for the masking the taste are currently utilized that not only provide pleasant taste but also good mouth feel. Sugars can be used as diluents and binders, as well as taste improving agents. For example, mannitol is one of the most common excipients for the RDT dosage form because it is water soluble, nonhygroscopic. An alternative method of taste masking is to encapsulate or coat the active ingredient with acceptable polymers or excipients.

Susan Z. Yanovski, 2003, In this study the author has tried to find a relationship between the Obesity and bing eating disorder. The author has the opinion that the BED could be a risk factor for an increase in the weight for non-obese patients. But, the challenge is to understand the ways in which bing eating disorder and Obesity exists together and find the management options that will control the disorder eating with enhance weight reduction. Often it is found that Obese patients with bing eating disorder can achieve weight loss, but find it rather difficult to maintain the reduced weight. This study results have delineated that obesity treating agents in combination with an antidepressant like VNF has effectively controlled the bing eating disorder along with reducing weight. Especially the combination approach could be very effective in controlling the weight regain in the individuals struggling with obesity and bing eating disorder. Further the eating patterns and depression level was significantly improved after the treatment for a period of six months. Therefore, the combination medication
therapy may provide a new means of reducing the weight and maintaining the weight in the obese individuals with binge eating disorder.

- **T Florence and D Attwood 2006**, A solution can be defined as a liquid system in which solute molecules (such as a drug or protein) are dissolved in a solvent vehicle. When a liquid solution contains a solute that can be maximum dissolved at room temperature and pressure, is called a saturated solution. When the solubility of the solid particles is exceeded its limit, and the solution phase will be in equilibrium with the solid. The saturated solubility of an active pharmaceutical ingredient in a given liquid medium is of pharmaceutical dosage form development interest. The solubility governs the rate of dissolution (formation of a solution) of the drug. The higher the solubility, the rapider is the formation of the solution when no chemical reaction is involved. Solvation is the general term used to describe the process of binding of solvent to solute molecules. When the water is the solvent, the process is hydration. pH is the primary factor that influences the solubility of many drugs that have an ionizable atoms. As the great majority of drugs are organic electrolytes, there are four parameters that determine their solubility. The solubility of small molecules in biological membranes is of importance from pharmacological, physiological and toxicological viewpoints. Biological membranes are not simple. The use of the mixed solvent device is adopted when the drug solubility in a single liquid is limited or when the stability of soluble salts perhaps limits the use of single solvents. Pharmaceutical formulations include glycerol, propylene glycol, ethyl alcohol and polyoxyethylene glycols. The addition of another component complicates any system and explanations of the often complex solubility patterns are not easy. In a recent, there has been any attempt to predict solubility in mixed solvents theoretically, although the solubility parameters of the mixed solvent systems has been purposed and used for some time. The solubility of the drug in the water or aqueous media may be markedly dependent on the salt form. The chemical stability rather than the solubility may be a criterion and in many cases this is dependent on the choice of salt, sometimes through a pH effect. The drug molecules or solute substances movement from one phase into the another is
called partitioning. The partitioning of the solute molecules and the calculation of the log P (partition coefficient) of the nonionized form of the solute (and its logarithm, log P), as well as the use of the log P concept in the determining the relative activities or toxicities of drugs from a knowledge of logP between an oil, most commonly octanol, and water. Where P cannot be measured, calculations of log P can be accomplished. The partition coefficient (log P) value is a measure of lipophilicity and the absorption of the drugs from the biological fluids depends on the lipophilic characteristics. Therefore a simple in vitro measurement of log P value can give an accurate assumption of absorption of a drug from the biological system, provided that the exact limitations of the system are recognized and the biological activity of the drug depends on its lipophilic nature. Applications of P or log P come into their own particularly in homologous series or series of closely related compounds, where the influence of substituent groups can be accurately examined.

- **Thomas et al., 2005**, the randomized controlled clinical trial study for one year, taking 224 obese adults was conducted to find weather medication like sibutramine 15mg per day alone or combination of medication and personal lifestyle changes will be beneficial for weight loss management effectively. In general, it has been observed that obesity treatment medication are prescribed as an adjunct to different comprehensive weight management programmes like exercise and behavioral therapy, but no change in the lifestyle modification will be recommended. In the study obese subjects who received sibutramine alone lost five to six kilogram of weight, those following the lifestyle modification alone lost lesser weight. The combination of sibutramine plus lifestyle modification seen to be reducing the weight more than either medication with sibutramine or lifestyle modification alone. Hence, a combination of medication with lifestyle modification would be an effective treatment for reducing the weight.

- **V. Ricca et al., 2009** in their study evaluated the overweight patients' psychopathological characteristics seeking weight reducing treatments. Their main findings were that overweight patients showed higher rate of psychiatric comorbidities, especially depression and anxiety and presence or severity of binge
eating was associated. Their study has confirmed the various previous findings by different authors that overweight or obese persons seeking the weight loss treatment generally have comorbid mental disorder. Emotional eating or eating due to psychological distress is correlated with the extent and severity of binge eating. In conclusion, they suggest that an accurate psychopathological investigation of the obese patients need to be performed and the treatment has to be focused on the targets eating disorder or emotional eating apart from the conventional weight loss treatments.

- **Vikas Agarwal et al., 2007**, Orally disintegrating tablets (ODTs) dosage forms, also generally known as rapid dissolving, fast melting, fast disintegrating, quick melts, and orodispersible dosage forms have the unique characteristic of disintegrating in the mouth within seconds. Especially for the acute conditions, this dosage form is preferred and easier for patients to take anytime, anywhere when the symptoms occur. For chronic condition treatment, it is believed to improve the patient compliance. There are many advantages of orally disintegrating tablets drug delivery systems compared to the other dosage form are the ease of taking the medication anytime without the need of water and ease of swallowing for patient's convenience. But, the limitations include difficulty sometimes in masking the bitter taste. Taste masking of an API may be achieved using number of techniques currently. However the excipients manufacturers are now supplying excipients specifically geared toward manufacture of ODTs. One of them is a spray-dried mannitol. The properties of this excipient suitable for ODTs include good compressibility at low hardness and fast disintegration, desirable properties for the manufacture of ODTs. The two brands commercially available include Pharmaburst by SPI Pharma and Pearlitol by Roquette.

- **W. M. Saltzman, 2001**, Pharmaceutical technology advanced, particularly after the 1970, methods of drug and vaccine production became more sophisticated and rational. In parallel with the rise of modern pharmaceutical technology and the explosive ascent of biotechnology, the effectiveness of drug action in the cellular and molecular basis has been discovered. Today, drug designers benefit from an accumulated base of scientific knowledge concerning, for example, the
interactions between neurotransmitters and their receptors, the regulation of hormone secretion, and the sensitivity of tumor cells to specific kinds of chemicals. New technology and clearer biological insight have led to new classes of therapeutic and prophylactic agents. This wealth of new technology and the resulting new armaments in the war against disease will incite new strategies for new drug dosage forms.

► **Yihong Qin et al., 2009**, described the various approaches used to develop the solid modified release dosage form like; Trial and error method, Semi empirical method and rational method. Among these the ration method of MR product development, approach is getting popular in the recent years. The rational method requires the consideration of three essential areas; initially the characterization or evaluation of the purity of the active and nonactive ingredients, compatibility studies, physical and chemical analysis are carried out prior to the formulation development. Further the formulation design and optimization is done by trial and error method, semi empirical or by modern quality by design methodology. This process will ensure the good quality of any solid dosage form with better drug delivery and pharmacokinetic performance.
Literature Review of the Active Pharmaceutical Ingredients or the APIs used in the Project Work:

2.3 Orlistat (ORL)

**Generic name**
ORL

**Chemical name**
(S)-2-formylamino-4-methyl-pentanoic acid-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester.

**Chemical Formula:** $C_{29}H_{53}NO_{5}$

**Molecular Weight:** 495

**Chemical Structure of ORL:**

![Chemical Structure of ORL]

**State:** Solid

**Description**
ORL is a slightly white to off-white crystalline powder

**Solubility**
ORL is practically insoluble in water, freely soluble in chloroform, and very soluble in methanol and ethanol.

**DMSO:** Solubility is 19 mg/mL

**BCS Class:** Class II

**Log p:** 8.6

**Melting Point**
Melting point is in the range of 46° to 48°C.
**Category**
Anti-Obsity Agent, Gastric lipese enzyme Inhibitor

**Dosage**
ORL 60 and 120 mg dose capsules are available. The recommended dose of ORL is 120-mg two-three times a day with each main meal containing fat (during or up to 1 hour of the meal).

ORL is a reversible lipases inhibitor. It shows the therapeutic activity locally in the gastrointestinal tract by forming a covalent bonding with the pancreatic and gastric lipases. (Xenical, 2000).

Table-03 Pharmacokinetic Parameters of ORL:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bvailability (oral) (%)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Renal Excretion</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Bound to Plasma protein (%)</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Clearance (ml. min-1.kg-1)</td>
<td>10.4 ± 1.1;</td>
</tr>
<tr>
<td>Half-Life (hours)</td>
<td>1-2</td>
</tr>
<tr>
<td>Peak Time (hours)</td>
<td>8</td>
</tr>
<tr>
<td>Peak Concentrations</td>
<td>&lt;5-10 ng/ml</td>
</tr>
</tbody>
</table>

**Mechanism of Action:**
ORL is a non-systemically acting drug that works locally to inhibit GI lipases and block or prevent the absorption of about 30% of dietary fat. Triglycerides are the major fat in food. They are composed of three fatty acid tails, with a glycerol backbone. In this form, they cannot be absorbed. Pancreatic and gastric lipases are the primary enzymes involved in the metabolism and absorption of dietary fat. In the small intestine, lipases cleave the
Cleave the triglyceride molecule, splitting off the fatty acid tails from the glycerol backbone. ORL binds to lipase, preventing it from breaking down triglycerides. The broken-down components of the triglycerides are then absorbed. The deactivated enzymes will be not able to hydrolyze the fat present in the form of triglycerides to free absorbable monoglycerides and fatty acids. The triglycerides present in the diet cannot be absorbed and are subsequently excreted in the feces. This results in the less calorie absorption and reduction in the weight. Therefore systemic absorption of the drug is not required for the therapeutic activity. ORL has a capability of inhibiting or reducing more than 30% absorption of the fat in the diet, making it one of the most effective drugs currently available (Zhi J, et al., 1995).

**Pharmacokinetics (ADME):**

**Absorption:** Systemic exposure to ORL is minimal. However systemic absorption of the drug is not needed for activity. Approximately 1% of ORL is systemically absorbed, with single-dose studies showing plasma concentrations of intact ORL < 5 ng/ml after a single dose of 800 mg. Bioavailability is 5% or less.

**Distribution:** In vitro ORL was >99% bound to plasma proteins (lipoproteins and albumin)

**Metabolism:** Metabolism of ORL occurs mainly within the gastrointestinal track. Two metabolites, M1 (4-member lactone ring hydrolyzed) and M3 (M1 with N-formyl leucine moiety cleaved). M1 and M3 have an open β-lactone ring and extremely weak lipase inhibitory activity (1000- and 2500-fold less than ORL, respectively). In view of this low inhibitory activity and the low plasma levels at the therapeutic dose (average of 26 ng/mL and 108 ng/mL for M1 and M3, respectively, 2 to 4 hours after a dose), these metabolites are considered pharmacologically inconsequential. The primary metabolite M1 had a short half-life (approximately 3 hours) whereas the secondary metabolite M3 disappeared at a slower rate (half-life approximately 13.5 hours). In obese patients, steady-state plasma levels of M1, but not M3, increased in proportion to ORL doses.
Elimination: Fecal excretion of the unabsorbed drug was found to be the major route of elimination. ORL and its M1 and M3 metabolites were also subject to biliary excretion. Half life is 1–2 hours.

Pharmacodynamics: Based on faecal fat measurements, the effect of ORL 120 mg three times daily is seen after two days of treatment. On discontinuation of treatment, faecal fat usually returns to baseline, within 48–72 h. The inhibition of dietary fat absorption by ORL is dose dependent. There is little additional effect on faecal fat excretion at doses greater than 360 mg daily and the recommended dose is one 120 mg capsule three times daily.

Side Effects: Changes in bowel function frequently occur because of the unabsorbed fat. Fatty/oily stool, oily spotting, intestinal gas with discharge, a feeling of needing to have a bowel movement right away, increased number of bowel movements, or poor bowel control may occur commonly. Headache, upper and lower respiratory infection, urinary tract infection, hypoglycemia, influenza, fatigue, menstrual irregularity, anxiety are the minor and rare side effects.

Indications and Usage
ORL is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. ORL is also indicated to reduce the risk for weight regain after prior weight loss. ORL is indicated for obese patients with an initial body mass index (BMI) 30 kg/m² or 27 kg/m² in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia).

Overdosage
Single doses of 800 mg ORL and multiple doses of up to 400 mg three times a day for 15 days have been studied in normal weight and obese subjects without significant adverse findings. Should a significant overdose of ORL occur, it is recommended that the patient be observed for 24 hours. Based on human and animal studies, systemic effects attributable to the lipase-inhibiting properties of ORL should be rapidly reversible.
2.4 Bupropion Hydrochloride (BPN Hcl.)

Chemical Name: 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone Hcl.
IUPAC Name: 2-(tert-butylamino)-1-(3-chlorophenyl) propan-1-one

Chemical Formula: C₁₃H₁₈ClNO•HCl.

Molecular Weight: 276.2.

Chemical Structure:

Melting Point: 234ºc

State: Solid

Appearance: It is a slight whitish crystallin powder. It is a bitter tasting substance producing the loss of sensation of the tongue due to local anesthetic effect

Solubility: 312 mg/ml in H₂O. It is freely soluble in water, 0.1N hydrochloric acid, Alcohol.

BCS Class: Class I

LOG P: 3.26
Mechanism of Action:
BPN Hcl. is an antidepressant that acts via dual mechanism of inhibiting both norepinephrine and dopamine reuptake in the CNS. Its antidepressant efficacy is similar to the SSRIs but with an advantage of less or no drowsiness and weight reduction (Stahl et al., 2004).

Absorption:
BPN mechanism of action is by activating the monoaminergic action in the CNS and inhibiting neuronal reuptake of norepinephrine and dopamine so that their concentration in the synaptic cleft is increased (Baldessarini RJ, 2001).

Metabolism and Excretion:
BPN Hcl. undergoes extensive hepatic metabolism by CYP2B6 through oxidation and reduction reactions prior to excretion. It produces three metabolites hydroxyBPN, threohydroBPN and erythrohydroBPN. Among this hydroxyBPN is the major metabolite. All the three metabolites even though they are less potent than the original BPN, they are also pharmacologically active ((Faucette et al., 2000, L. Dwoskin et al., 2006).

Dose: 75 mg to 450mg/day.

BPN Hcl. Pharmacokinetic and Pharmacodynamic Properties: (L. Dwoskin et al., 2006).

Table-04 Pharmacokinetic Parameters of BPN Hcl.:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bavailability (oral)</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>Bound to Plasma protein</td>
<td>84%</td>
</tr>
<tr>
<td>Apparent Clearance</td>
<td>160 L/hr</td>
</tr>
<tr>
<td>Half-Life</td>
<td>10–20 h</td>
</tr>
<tr>
<td>Peak Time (Tmax)</td>
<td>~2 h,</td>
</tr>
<tr>
<td>Peak Concentrations (Cmax)</td>
<td>136 ng/mL</td>
</tr>
</tbody>
</table>
Pharmacodynamics: BPN, an aminoketone class of antidepressant. It is a dual noepinerphrine and dopamine reuptake inhibitor. BPN does not inhibit monoamine oxidase. Thus it enhances activity of monoaminergic by prolonging the concentration of norepinaphrine and dopemine in the synaptic cleft. It’s antidepressant activity is equivalent to SSRIs and tricyclic antidepressants. And the mechanism of action of BPN has no serotonergic effect, for this reason it has no erectile dysfunction in the males.

Indications: All depression disorders, anxiety disorders and Smoking cessation.

Side Effects: Nausea, dry mouth, restlessness, headache, constipation, agitation, insomnia, skin rash and tremor. BPN overdose is reported to cause the seizures.
2.5 Venlafaxine Hydrochloride (VNF Hcl.)

VNF is the first antidepressant drug of serotonin noradrenaline-reuptake inhibitor (SNRI) class.

**Chemical name:**
1-[2-(dimethyl-amino)-1-(4-methoxyphenyl)-ethyl]cyclo-hexanol hydrochloride

**IUPAC name:**
1-[(1RS)-2-(Dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclo-hexanol hydrochloride

**Chemical formula:** $C_{17}H_{27}NO_{2} \cdot HCl$

**Chemical Structure:**

![Chemical Structure Image]

**Melting Point:** 215-217°C

**State:** solid

**Appearance:** white to slightly white crystallin solid

**pKa:** 9.4

**Solubility:** 572 mg/mL in water. It is freely soluble in water, methanol and dilute hydrochloric acid, soluble in ethanol and chloroform and insoluble in ether.

**BCS Class:** Class I
Log p: 2.8

Pharmacokinetics: (Burnett and Dinan 1998).

Absorption:
VNF is absorbed very well after oral administration. It reaches the peak plasma concentration within one or two hours. The bioavailability of the intact VNF is 45%. VNF efficacy is similar to the tricyclic and SSRI antidepressants in the treatment of major depression. VNF and its major metabolite O-demethylVNF (ODV) are minimally bound to plasma proteins approximately 27% and 30%, respectively at therapeutic concentrations.

Metabolism and Excretion:
VNF undergoes extensively first pass metabolism in the liver. VNF is the double inhibitor of both serotonin and noradrenaline resulting more rapid onset of antidepressant effect. It is metabolized primarily in the liver by the enzyme CYP-450 to produce major active metabolite O-demethylVNF (ODV) and less active metabolites, N,O-didemethylVNF and N-demethylVNF. However, its major active metabolite O-demethylVNF (ODV) has the same antidepressant effect as the original VNF therefore there is not much effect on its efficacy. Elimination of VNF and its metabolites is primarily by renal route.

Dose: 75 to 375 mg/day.


Table-05 Pharmacokinetic Parameters of VNF Hcl.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability (oral)</td>
<td>45%.</td>
</tr>
<tr>
<td>Apparent Clearance</td>
<td>1.3±0.6L/h/kg</td>
</tr>
<tr>
<td>Bound to Plasma protein</td>
<td>27%</td>
</tr>
<tr>
<td>Mean Vol. Distribution</td>
<td>7.4±1.6 L/kg</td>
</tr>
<tr>
<td>Half-Life</td>
<td>4h</td>
</tr>
<tr>
<td>----------</td>
<td>----</td>
</tr>
<tr>
<td>Peak Time (Tmax)</td>
<td>1-2 h</td>
</tr>
<tr>
<td>Peak Concentrations (Cmax)</td>
<td>150 ng/mL</td>
</tr>
</tbody>
</table>

**Pharmacodynamics:**

VNF and its active metabolite, O-desmethylVNF (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. VNF activates the monoaminergic function by enhancing and prolonging the concentration of serotonin and norepinephrine in the synaptic cleft. Thus, potentiating of neurotransmitter activity in the CNS is done.

**Indications:**

All depression disorders, anxiety disorders and eating disorders.

**Side Effects:**

Very common side effects are Nausea, dry mouth, headache, dizziness and sweating. Common side effects are confusion, constipation, insomnia, eyesight problems, dizziness, nervousness, hot flushes, impotence, loss of appetite, hypertension, somnolence, tiredness, tremors, urinary problems, vasodilatation, vomiting, weakness and weight loss.