CHAPTER-06

6.1 SUMMARY AND CONCLUSION

6.1.1 Introduction

Obesity is an epidemic disease according to the latest WHO report. From the vast literature survey it is confirmed that, the increase in calorie intake or excessive eating is the main culprit for the rising obesity, in comparison to the other aspects (WHO Obesity factsheet, 2014, B. Rospond et al., 2015). Many clinical studies have reported increased appetite, overeating or bing eating and reduced physical activity in obese subjects. (Carter et al., 2003, JA Linde et al., 2004). For this reason, obese individuals are more prone to have coronary heart disease, dyslipidemia, stroke and diabetes. Most of the researchers are of the opinion that increases in calorie intake or excessive eating is the main culprit for the rising Obesity, in comparison to other aspects. (Bray et al., 2004, Lewis Landsberg et al., 2013). The high qty. food eating or bing eating is the parvalence of psychological depression among obese patients. More than fifty percent of severely obese patients suffer from psychological distress or depression. And the obese patients with depression are usually accompanied by the bing eating disorder (G. T. Wilson et al., 1993, F.S. Luppino et al., 2010). Bing eating disorder is an eating disorder a huge qty. of food in a short period, and the sufferer will be unable to control the carving for the high-calorie rich food (Renu Kotwal et al., 2004, JA Linde et al., 2004). In the last two decades Obesity and bing eating disorder or over eating have became a big challenge for the physicians treating the obese patients (V. Hainer and Hainerov 2012, J.C Seidell 2014). The successful management of the excess weight in the obese patients, it is necessary to emphasis on the management of bing eating disorder as part of weight management strategy. Because, treating the psychological distress in obese patients will not only helps in controlling the bing or excessive eating pattern but, also controls and reduces the weight (Michael J. Devlin, 2001, Pokrajac-Bulian et al., 2013). In the present scenario, there should have been many pharmacotherapies for the treatment of Obesity. But at this situation ORL is the single medication available and registered by US for the
management of Obesity and available commercially in 60mg and 120mg as capsules (Kakkar and Dahiya 2015). Recently FDA approved combination of Naltrexone-bupropion (Contrave), phase III clinical trials were conducted for fifty six weeks in the contrave Obesity research (COR). The results of this clinical trial have proven that the new combination is capable of both reducing the weight and also controls the food intake or binge eating pattern in the obese individuals (S.K. Billes et al., 2014, Wang GJ, et al., 2014). For this reason compared to monotherapy, a combination therapy could be better option for the treatment of Obesity and depression with binge eating disorder (Devlin MJ 2001, Rothman R. B, 2009).

6.1.2 Chewable Tablets

Chewable tablets are one of the oldest and most ignored dosage forms. But again in the today’s generation the importance of this PDF is being realized, because it can be easily chewed similar to any toffes and does not have bad unacceptable feel in the human senses. These tablets are formulated and manufactured by compression generally utilizing sweet tasting excipients like, sucrose, Sorbitol or Mannitol as fillers and binders along with flavors and colors to enhance their palatability. Chewable tablets when chewed or sucked and swallowed will provide local effect in the gastrointestinal tract, or be absorbed through the GIT for systemic action.

6.1.3 Mini-Tablets as fast disintegrating Chewable Tablets

Mini-tablets are novel single or multiple solid dosage form which are in the size equal to or smaller than three millimeter in diameter. Mini-tablets have many advantages compared to pellets and granules for example uniform in size and shape no multiple coating is required (Lennartz and Mielck, 1998 and Munday, 1994). Fast-dispersing or oral dispersing tablets must disintegrate the tablet in less than a minute into a suspension or solution form when comes in contact with the aqueous fluid. Fast-dispersing tablets are especially more acceptable and appreciated by people who have difficulty in swallowing. Further, the compression of the fast-dispersing mini tablets along with microparticles and excipients to prepare a stable tablet could be feasible and lucrative
technique. The mini tablets along with taste-masked microspheres or pellets are often mixed with other excipients to form orally disintegrating chewable tablets (Jianchen Xu et al., 2008, Xin Pan, et al., 2010).

6.1.4 Compression-Coated Chewable Tablets:
A compression-coated tablet is a solid dosage form, in which all the surface of an inner core tablet is completely covered by coat layers. Compression coating is mainly used to develop the combination of drugs and to protect the hygroscopic or unstable drug in the core by coating with the stable outer layers (Hariharan, M., Gupta, 2001). Compression coated chewable tablets can also be prepared successfully. For preparing the compression, coated tabled a rotary bi-layer tablet compression machine is more suitable. Therefore in this project formulation blends by direct compression was done using the bilayer compression machine.

6.1.5 Objectives:

- The purpose of the present research project was to develop and optimize the new formulations for the treatment of Obesity and binging disorder. With this objective three APIs were selected viz., Orlistat, Venlafaxine Hydrochloride and Bupropion Hydrochloride.
- Performing the pre-formulation studies including, characterization of the selected drugs and excipients. And to develop a HPLC method for the selected single API or combination of APIs.
- To design and develop the taste masked stable and efficacious dosage form with better patient compliance. Evaluate the different batches developed and optimize the formulation of different dosage forms. Finally to perform the short ninety days stability studies following the international guidelines of ICH.
6.1.6 METHODOLOGY

(I) Orlistat Orodispersible Mini-Tablets: Formulation and Evaluation

The purpose of this project was to prepare Orodispersible mini-tablets of ORL (ORMTs) that can disintegrate within a minute upon coming in contact with the aqueous fluid to enhance the patient compliance and the efficacy. In the preformulation work purity of the drug ORL was confirmed. There was no compatibility contradiction between the active and nonactive substances confirmed by FTIR. The liquid chromatographic method is developed and validated utilizing the reverse phase mobile liquid running at flow of 1.5ml for twelve minutes and the retention time was found to be at 9.4 minutes. In the solubility enhancement of ORL complexed with β-CD in one is to two molar ratio was found more beneficial and was increasing the solubility from 1.91± 0.171 mg/ml to 8.81± 0.261 mg/ml. The crystalline state of Orlistat pure and Orlistat-β-CD complex is characterized by the XRD and no change in the spectrum was found.

Then in the optimization of formulation nine formulations trials were carried out using different novel co-processed excipients. Pre and post compression evaluation of all the formulation was done. All the results were found to be within the standard limit. Based upon the results obtained the formulation (ORMT-9), which was prepared using ludiflash 40% was found to be disintegrating rapidly and releasing the ORL at regular intervals. Therefore (ORMT-9) formulation was chosen as the optimized formulation of ORMTs. Further the optimised formulation (ORMT-9) was compared with the existing marketed capsule where, it was found to releasing faster than the capsule. In the application of different models of kinetics to the libration of drug form the optimised (ORMT-9) seen to follow the first order kinetics. Finally in the evaluation of taste it was found to be incredibly palatable with no objectionable taste and odour. Hence, the prepared and optimised ORMTs have passed all the quality control tests and are therefore recommended for the clinical human studies. Once clinical study bioequivalence test is passed, it can be applied as a generic dosage forms. Optimised ORMTs are small and lucrative dosage form that can be easily carried as sachet dosage form and swallowed directly just after dispersing on the tongue or can be taken with any foods or drinks and
hence there is good possibility of becoming a better substitute for the existing ORL capsule dosage form.

(II) Development of Combination Chewable Mini Tablets-In-Tablet of Orlistat and Bupropion Hydrochloride

The purpose of this project was to prepare the dispersible mini-tablets of Orlistat (ORL) and compress along with the taste masked Bupropion (BPN) Hydrochloride to develop a combination of chewable mini tablets-in-tablet. ORL is an anti-Obesity drug and BPN Hcl. is an antidepressant drug also prescribed for the cessation of smoking and eating disorder. ORL-β-cyclodextrin (1:2M) complexed dispersible mini-tablets of 3mm size each containing 6mg ORL, were prepared and optimized previously in the 1st methodology are used here. Ten mini-tablets containing 60mg ORL are taken and compressed with taste masked 100mg Bupropion Hcl. Microspheres [prepared with Eudragit EPO (1:3), by emulsification solvent evaporation method].

The liquid chromatographic method is developed and validated utilizing the reverse phase mobile liquid following the guidelines described by ICH for the simultaneous estimation of ORL and BPN in the formulation. The chromatographic combined active substances development was performed on an Altima C 8 column using the movable solution consisting of Acetonitrile and pH3 buffer. The detection in the UV was done at 210nm. The movable solution in the ratio of (82.5-17.5), was flowing at a rate of 1.2 ml/min running for twelve minutes. Further, formulations were designed and combination chewable mini-tablets-in-tablet are developed by taking ten mini-tablets of ORL containing 60mg of ORL and taste masked microparticles of BPN equivalent to the 100mg BPN along with other excipients. Six formulation trials were carried out to optimize the chewable mini tablets-in-tablet formulation. There was no compatibility contradiction between the active and nonactive substances in the PDF which was confirmed by overlapping the spectr of FTIR. The compression of different formulation blends was done by direct compression method using the Karnavathi’s Minipress II DL bilayer tablet compression machine. Ultimately, the formulation OBT-T-6 containing the
20% of Ludipress was found to be releasing approximately 80% of both ORL and BPN within the first fifteen minutes. And also the optimized OBTT-6 formulation in the taste evaluation and stability studies was found to be satisfactory. When the different kinetic models are applied to the drug release profile of both ORL and BPN from the OBTT-6 formulation it was best fitting with the first order kinetics indicating the good immediate release chewable dosage form. Hence, the developed and optimized chewable mini tablets-in-tablet of ORL and BPN can be excellent patient compliance dosage form for treating obese patients with psychological distress or depression.

(III) Chewable Press Coated Tablets of Orlistat and Venlafaxine Hydrochloride- Development and Evaluation

In this project a dispersible 60mg complexed with β-CD in one is to two molar ratios complex containing equivalent to 60mg ORL is taken and dispersible core tablets is press coated with the taste masked VNF microparticles, containing the VNF equivalent to 75mg (prepared with Eudragit EPO in one is to three molar ratio applying the by emalsification and evaporation method), to obtain the chewable press coated tablets dosage form. Then the liquid chromatographic method is developed and validated utilizing the reverse phase mobile liquid running at flow of 1.5ml for twelve minutes. There was no compatibility contradiction between the active and nonactive substances used. To obtain the optimized formulation six formulation trials of core tablet and the coating layers were done in the lab. All the trial batches led for recommended tests.

As noted earlier ORL is a very hydrophobic and a difficult drug to prepare tablets. Therefore to enhance the solubility and make it suitable for preparing tablets complexation with β-cyclodextrin in different ratios was done in the preformulation study. VNF is a very bitter taste drug, to make it suitable for the chewable formulation different efforts of taste masking viz. complexation with β-CD, solid dispersions and microencapsulation with Eudragit EPO in different ratios were tried. Among them VNF microencapsulation with eudragit EPO in the ratio of 1:3 was found to be more effective in masking the bitter taste and was chosen for formulation of coating layers. Further, to
obtain the optimised formulation of ORL and VNF chewable press coated tablets, six formulation trials of ORL dispersible core tablets and six formulation trials of VNF coating layers were carried out. The drug and the different excipients compatibility was confirmed by IR spectra. The compression of different formulations blends was done by direct compression method using the Minipress II DL bilayer tablet compression machine of Karnavathi’s. Primarily the ORL dispersible core tablets was optimised, based upon the results obtained the core tablet formulation ORC-2, which contains novel coprocessed excipients i.e., Ludiflash 14% and Kollidon CLF 4.5% was chosen as optimised inner core tablet formulation. The ORC-2 formulation was found to disintegrating within two minutes and releasing the 90% of drug in 10mins. Further, taking a placebo core tablet, six formulation trials of outer coating layers were carried out. And the outer layers formulation VLC-5 was chosen as the optimized coating layer formulation as it was masking the taste effectively without affecting the release of drug. Then, taking ORC-2 inner core and VLC-5 outer coating layers, the optimised formulation of chewable press coated tablets (OPCT) were compressed. The physico-chemical evaluation results of (OPCT) formulation were found to be within the standard limits. In the in-lab drug libration test, the release of both ORL and VNF at the end of fifteen minutes was found to approximately ninety percent. More importantly the optimized (OPCT) formulation in the taste evaluation and stability studies was found to be satisfactory.

When the different kinetic models were applied to the drug release profile of the both ORL and VNF from the (OPCT) formulation it was best fitting with the first order kinetics indicating the good immediate release chewable dosage form. Hence, the developed chewable press coated tablets of ORL and VNF can be an excellent chewable dosage form for treating obese binge eaters suffering from depression.
6.1.8 GENERAL CONCLUSION

Obesity the fast growing epidemic is caused due to increased calorie intake without doing enough physical activity. The literature available has confirmed that, the increase in calorie intake or excessive eating is the main culprit for the rising obesity, in comparison to the other aspects. In addition, more than fifty percent of severely Obese patients suffer from psychological depression. And the obese patients with depression are usually accompanied by the symptoms of bing eating disorder. The purpose of the present research project was to develop and optimize the novel chewable dosage forms for the treatment of Obesity and bing eating disordr . With this objective three APIs were selected viz., Orlistat, Venlafaxine Hydrochloride and Bupropion Hydrochloride. ORL a lipatic inhibitor is the only US approved medicine for Obesity for longer course. VNF Hcl. and BPN Hcl. are antidepressants also prescribed for the treatment of Bing eating disorder. Primarily the preformulation study including the physico-chemical characterization was carried out. The results were compared with the reference standard, and the results were found to be within the standard limits. Further, according to the plan of work three different dosage form formulations are developed, evaluated and optimized.

(I) Orlistat Orodispersible Mini-Tablets: Formulation and Evaluation

The purpose of this project was to prepare orodispersible mini-tablets of ORL (ORMTs) that can disintegrate within a minute upon coming in contact with the aqueous fluid to enhance the patient compliance and the efficacy. In the preformulation work purity of the drug ORL was confirmed. There was no compatibility contradiction between the active and nonactive substances which was confirmed by FTIR. The liquid chromatographic method was developed and validated utilizing the reverse phase mobile liquid technique. ORL is a very low aqueus soluble drug and it shows action locally. However, irrespective of the site of action a high solubility of drug is recommended for the rapid libration of the drug from the dosage form. For this reason different techniques of enhancing the solubility and stability of ORL were done in the lab. In those methods tried ORL complexed with β-CD in one is to two molar ratio was found more beneficial and was
increasing the solubility quite well and has good compatibility to prepare the ORL dispersible mini tablets.

Then to optimize the ORL dispersible mini tablets dosage form, nine trials were carried out using different co-processed excipients and excipients. Pre and post compression evaluation of all the formulation was done. All the valued were comparable with the standard limit. Based upon the results obtained the formulation (ORMT-9), which was prepared using ludiflash approx. forty percent was found to be disintegrating rapidly and liberating the ORL at regular intervals almost ninety percent within the first ten minutes. In the evaluation of taste optimised formula was found to be palatable with no objectionable characteristics. Hence, the ORL orodispersible mini-tablets were prepared and optimised.

(II) Development of Combination Chewable Mini Tablets-In-Tablet of Orlistat and Bupropion Hydrochloride

The purpose of this project was to prepare the dispersible mini-tablets of ORL and compress along with the taste masked BPN Hcl. to develop a combination of chewable mini tablets-in-tablet for the treatment of Obesity and depression. ORL dispersible mini-tablets were prepared earlier in methodology-I are used here. Ten mini-tablets containing 60mg ORL are compressed with taste masked 100mg BPN Hcl. Microspheres [prepared with Eudragit EPO (1:3), by emulsification solvent evaporation method]. The liquid chromatographic method was developed and validated utilizing the reverse phase mobile liquid technique for estimating the ORL and BPN Hcl. in the formulation. The optimized formulation (OBTT-6) was found to be palatable and there was no compatibility contradiction between the active and nonactive substances that confirmed by FTIR. Chewable mini tablets-in-tablet were evaluated for all the required standard tests. The findings of tests values were within the limits. And in the in-lab drug libration studies both drugs i.e., ORL and BPN at the end of 15mins were found to be releasing 75 % and 85% respectively. And also the optimized OBTT-6 formulation in the taste evaluation and stability studies was found to be satisfactory. When the different kinetic models were applied to the drug release profile of both ORL and BPN from the OBTT-6 formulation it was best fitting with the first order kinetics indicating the good immediate release.
chewable dosage form. Hence, the developed combination chewable mini tablets-in-tablet formulation of ORL and BPN Hcl. can be good patient compliance dosage form for treating Obesity with co-morbid depression.

(III) Chewable Press Coated Tablets of Orlistat and Venlafaxine Hydrochloride-Development and Evaluation

In this project a dispersible 60mg complexed with \( \beta \)-CD in one is to two molar ratios complex containing equivalent to 60mg ORL is taken and dispersible core tablets is press coated with the taste masked VNF microparticles, containing the VNF equivalent to 75mg (prepared with Eudragit EPO in one is to three molar ratio applying the by emulsification and evaporation method,) to obtain the chewable press coated tablets dosage form. Then the liquid chromatographic method is developed and validated utilizing the reverse phase mobile liquid running at flow of 1.5ml for twelve minutes. There was no compatibility contradiction between the active and nonactive substances used. To obtain the optimized formulation six formulation trials of core tablet and the coating layers were done in the lab. All the trial batches led for recommended tests. Based on the results values ORC_2 was the optimized ORL dispersible core tablet and the formula VLC_5 as the coating layer were chosen. Further taking this two the optimized formulation (OPCT) compression was done by direct compression method using the Minipress II DL bilayer tablet compression machine of Rimek K. The optimized (OPCT) Chewable Press coated, tablets were evaluated for physicochemical properties and none of the test was failed and all the results were within the limits. And in the in-lab drug libration study the release of both drugs, ORL and VNF at the end of one fourth hour was found to be liberating nearly ninety percent. Finally in the crucial taste evaluation the volunteers response was satisfactory as shown in the results. Hence, the developed chewable press coated tablet formulation of ORL and VNF can be an effective and viable chewable dosage form for treating obese patients with bing eating disorder.

In the conclusion, recent years research has proven that the Obesity may cause depression; through the negative body image. Occurrence of depression in Obesity is the potential contributor of bing eating disorder that causes lack of control over eating leading to excessive eating. Therefore, Obesity in association with bing eating disorder could be
lethal for overly obese patients who desire to lose weight. Currently, ORL is the only drug registered and approved by FDA for the long term course of Obesity. And few anti-depressants like SSRIs, VNF and BPN have proven efficacy in the treatment of depression and bing eating disorder. But, all these medications are at present available in the market only as capsules or tablets. Hence there is a wide scope in the future for the novel chewable dosage form formulations developed and optimized in this research project.
6.2 RECOMMENDATIONS

The extensive literature survey has confirmed that there is an urgent requirement of novel single or a combination therapy for the Obese patients with binge eating disorder and depression. In the present scenario, there should have been many pharmacotherapies for the treatment of Obesity and depression with BED. Even then at present only few monotherapy and combination therapies approved by FDA are commercially available. Recently few uncontrolled clinical trial data has been reported and the results have been encouraging which, clearly showed that the novel combination pharmacotherapy is effective and safe. The novel FDA approved combination of Naltrexone-bupropion (Contrave), clinical trial study was conducted for fifty six weeks in the contrave Obesity research (COR). The results have proven that this novel combination is not only capable of reducing the weight but also controls the food intake or binge eating pattern in the obese patients (S.K. Billes et al., 2014, Wang GJ, et al., 2014). For this reason, compared to monotherapy a combination therapy could be better for the treatment of obese binge eaters suffering from depression (Devlin MJ 2001, Rothman R. B, 2009).

In the research project presented in the dissertation, an attempt has been made with the available medication for Obesity and binge eating disorder to prepare and optimize attractive and palatable oral chewable dosage forms of both single and combination medication. So that the Obesity and binge eating disorder, treatment adherence can be increased in the obese binge eaters suffering from depression. However, further clinical trials if possible in healthy subjects should be conducted to ascertain that there is no unexpected harmful response from the developed and optimized chewable dosage forms. And also, further investigation of more combination treatments under randomized, double-blind conditions is recommended. Especially the clinical trials comparing combination therapy with that of monotherapy are required and rational treatment guidelines need to be framed.
6.3 FUTURE SCOPE OF THE WORK

Obesity and its associated comorbid diseases are estimated to cost more than the $100 billion directly or indirectly health costs worldwide annually. But still the treatment of Obesity and eating disorder are below par and there is a lot of scope for its growth. All the data and reports tend to showcase that Obesity and eating disorders especially the binge eating disorder continues to be a challenge even for the best medical experts in the well established and sophisticated medical centers (Stevns et al., 2012, Keats & Wiggins, 2014).

The vast clinical research done on Obesity over the last few decades have proven that, the depression and binge-eating disorder more frequently co-exists with the Obesity. And the patients who are suffering from this comorbid condition have shown no or less interest in taking the prescribed medications. Hence, in the present project an attempt has been made with the available drugs for the treatment of Obesity and physiological disorders to prepare and optimize an attractive and palatable oral chewable dosage forms. Both single and combination dosage form formulations have been developed and optimized, with an objective to enhance the clinical efficacy and treatment adherence for the obese patients suffering from the binge-eating disorder due to depression. However, as it has been noted in the future recommendations, that the randomized, double-blind clinical trials must be conducted for the optimized formulations. And if the clinical trials in humans are conducted as per the specified guidelines and optimized formulations are proven safe and efficacious. Then, there is a wide scope for the new chewable dosage form formulation developed in this project work for the treatment of Obesity and bing eating disorder. More importantly because, the current medication available in the market for the treatment of Obesity and bing eating disorder are either in the form of capsules or tablets. Hence, there is a significant scope of this project getting recognized as novel chewable dosage form to make the medication more attractive and patient compliance with better therapeutic efficacy. Therefore the developed and optimized single or combination chewable dosage forms in this project once proven safe and effective in clinical studies, it will be very fruitful for the obese binge eaters suffering from depression.
6.4 LIMITATIONS OF THE RESEARCH WORK

Findings from the vast literature available related to Obesity study, the fact is clear that novel formulations for the obese patients with BED are the need of the hour. Realizing this from the literature survey the need for the good lucrative and palatable dosage form was felt. For this reason, this project was purposed to develop the novel chewable oral dosage forms that does not have limitations like bad odor and taste and also difficulty in swallowing for obese binge eaters suffering from depression.

With an objective of enhancing the palatability and patient compliance, the limitation of the developing the palatable chewable dosage form for the Obese binge eaters was considered as challenge and a scope to improve the oral solid dosage form design was felt. In the present research work an attempt has been made with the available drugs for the treatment of Obesity and physiological disorders to develop and optimize novel and palatable oral chewable dosage forms. The ultimate objective was to enhance the patient’s compliance and acceptability.

The limitations of the present project work were; the evaluation of the optimized formulations was confined to the in-vitro studies, because of lack of funding or donations from either the government or private institutions. However, this research project has been conducted in the labs with enormous facilities having sophisticated new equipments as listed in the equipment used list. In this research project, chewable dosage forms were developed and optimized in which the taste of the optimized formulation plays a very crucial role in the optimization. Now a days for the evaluation of the taste of a chewable pharmaceutical product a novel instrument called ‘electronic tongue’ is available and used by some multi-national companies. Therefore we tried to access and use this instrument for our optimized formulations but could not obtain the services. However, following high rated references of the conventional methods of taste evaluation, the taste evaluation studies were carried out with the help of the panel of taste evaluating human volunteers.