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Novel chewable tablet-in-tablet dosage form of Orlistat and Venlafaxine hydrochloride: development and evaluation

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ABSTRACT

Obesity is a chronic pathological condition characterized by an increased body fat accumulation to the extent that it may have an adverse effect on the health. Depression is the most common co-morbidity of obesity, which may cause the Binge Eating Disorder (BED), leading to morbid obesity. In the present project a dispersible 60mg Orlistat (ORST) and β-cyclodextrin (β-CD), (1:2M) complexed core tablet is press coated with the taste masked 75mg Venlafaxine Hcl. (VLFXN) microparticles, prepared with Eudragit EPO (1:3), by emulsification solvent evaporation method, to obtain the chewable tablet-in-tablet dosage form. A Reverse phase (RP)-HPLC method was developed for the simultaneous estimation of ORST and VLFXN in the formulation. The optimized formulation was palatable and there was no drug excipients interaction which was confirmed by IR Spectrum. Press coated, tablet-in-tablets were evaluated for physicochemical properties. All the values obtained were within the standard limits. And in the in-vitro dissolution study the release of both drugs, ORST and VLFXN at the end of 15mins was found to be 86% and 92% respectively. Hence, the developed chewable tablet-in-tablet formulation of ORST and VLFXN can be a viable drug delivery system for treating patients with obesity and BED.

INTRODUCTION

Tablets are the most popular dosage form and three-fourth of the total medicine is dispensed in the form of tablets. For those people who have swallowing problems, chewable tablets are the best alternative and most widely used chewable dosage form (Lachman, *et al.*, 1987 and Mary Kathryn *et al.*, 2002). A compression-coated tablet is a solid dosage form, in which all the surface of an inner core tablet is completely surrounded by coat layers. Compression coating is mainly used to develop the combination of drugs and to protect the hygroscopic or unstable drug in the core by coating with the stable outer layers, (Herbert A. Lieberman *et al.*, 1989). Recently, the drawback of compression coating, i.e., keeping the core tablet in the centre of the compression-coated tablets and absence of core in the coat, have been overcome by using novel compression tools in one-step dry coated tablet (OSDRC) by (Ozeki *et al.*, 2004 and Tokudome *et al.* 2009). Obesity is an abnormal or excessive fat accumulation that will impair health by causing the diseases (WHO, obesity factsheet, 2013). Overweight and obesity are the fifth leading cause for global deaths. Approximately three million adults die each year as a result of being overweight or obese.

According to a recent WHO global estimate nearly 1.5 billion adults all over the world are overweight (Constatine *et al.*, 2008, Statistics on obesity UK, 2013). Obese individuals are at an increased risk of coronary heart disease, stroke, dyslipidaemia and type II diabetes. Obesity may lead to diminished quality of life as the obese person tends to have negative body image (Ann Marie 2006, and Landsberg *et al.*, 2013).

Further, the obese person suffers from stigmatization and discrimination, leading to major depression. Therefore, high prevalence of binge eating disorder (BED) is found to be associated with the co-existence of obesity and depression (Dixon *et al.*, 2003). BED is defined as, eating large amount of food in a short period and a sense of lack of control over eating during the episode

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(i.e., a person cannot stop eating or control what or how much one is eating) (Wolfe BE *et al.,* 2009). An extensive literature survey of last four decades showed that there is a pathogenic association between obesity and depression, leading to binge eating disorder. This data is supported by various randomized clinical trials, which illustrate many patients suffer from obesity and BED. Therefore, the treatment of overly obese patients must need to address not only weight reduction. In addition, treatment should also address the symptoms of depression and binge eating disorder (Michael J. Devlin, 2001, Malhotra S *et al.,* 2002, Carter *et al*., 2003, McElroy SL *et al*., 2004, Reas and Grilo, 2008, Scholtz and Morgan, 2009). The objective of the present project was to enhance the solubility of ORST and mask the bitter taste of VLFXN to prepare a chewable press coated, tablet-in-tablet. ORST is a gastrointestinal lipase inhibitor; an anti-obesity drug and VLFXN is an antidepressant of the SNRI class, also prescribed for binge eating disorder.

MATERIALS

Orlistat and Venlafaxine Hcl. were the kind gift sample from RA Chem pharma Pvt Ltd. Hyderabad. Ludipress LCE, Ludiflash, Kollidon CLF and Kollidon-30 were the generous gift sample from BASF Pvt Ltd. Mumbai. β-cyclodextrin and Maltodextrin were procured from SD fine chem. Pvt Ltd. Mumbai. Sucralose, Cherry and Peppermint flavour were a gift sample from Cheminova Pvt Ltd. Hyderabad, Magnesium Stearate and Talc were procured from Qualikem fine chem. Pvt Ltd, Vadodara.

EXPERIMENTAL METHODS

Development of HPLC method for simultaneous determination of ORST and VLFXN in the formulation

A RP-HPLC method was developed and validated as per the ICH guidelines for the simultaneous estimation of ORST and VLFXN in the formulation. A Perkin Elmer 200 series HPLC System equipped with UV-detector using (Column Lichrospher® 100 RP-18e (5µm). The wavelength for UV detection was set at 210 nm. The mobile Phase was acetonitrile and Phosphoric acid buffer of pH3 in the ratio of (95:5), at the flow rate of 1.5 ml/min with run time of 12 mins.

Solubility enhancement of ORST

ORST is a highly hydrophobic and a hygroscopic drug, to enhance the solubility and stability; techniques like solid dispersion and Complexation with β-cyclodextrin in different ratios were tried in the preformulation study.

Preparation of ORST-Solid Dispersions by Solvent evaporation method

Solid dispersions of ORST with PEG-6000 containing four different ratios of (1:1, 1:2, 1:3 and 1:4) were prepared by the solvent evaporation method. ORST and the polymer were dissolved in a minimum quantity of methanol. The solvent was evaporated by slow stirring on a magnetic stirrer at the warm temperature, not above 40° C for 30 mins. The resulting residue was dried for 24h in a desiccator. After drying, the dry mass was ground in a mortar and sieved through sieve #60, labeled and stored in a desiccator until further use.

Preparation of Physical mixture (PM) and Inclusion complex of ORST

Physical mixing

Accurately weighed quantity of ORST was mixed thoroughly with β-CD in 1:0.5, 1:1, 1:1.5 and 1:2 molar ratios in the dry state. The mixtures were then passed through #60 sieve to have uniform size and stored in desiccator until further use.

Inclusion complex of ORST by kneading method

ORST β-cyclodextrin complexation in the molar ratio of (1:0.5, 1:1, 1:1.5 and 1:2M) was done by kneading method. Accurately weighed quantity of β-CD was placed in a mortar with few drops of water and kneaded to the paste consistency. Then weighed quantity of drug was introduced slowly and kneaded vigorously for 1h.

During this process, an appropriate quantity of water was added to maintain suitable consistency. Finally, the dry residue obtained was kept in a desiccator for 24h to remove the moisture. After drying completely, the dry mass was ground in a mortar and passed through sieve #60, labeled and stored in a desiccator until further use (Somagoni *et al.,* 2011).

Taste Masking of VLFXN

VLFXN is a very bitter taste drug, to make it suitable for the chewable formulation two different efforts of taste masking, complexation with β-CD and microencapsulation with Eudragit EPO in different ratios were tried.

β-CD Inclusion complex of VLFXN by kneading method

VLFXN-β-CD complexation in the (1:2, 1:3 and 1:4M) was done by kneading method as explained earlier.

Microencapsulation of VLFXN with Eudragit EPO by Emulsification solvent evaporation method

VLFXN microspheres were prepared by taking VLFXN and Eudragit EPO in the ratio of (1:1, 1:2, 1:3 & 1:4), and the microencapsulation was done by emulsification solvent evaporation method. In this method, required amount of drug is dissolved in acetone containing required quantity of polymer with constant stirring for 30 minutes. Then, this solution is slowly dispersed into 100 ml of heavy liquid paraffin containing 1%w/w tween 80 in a beaker, at a stirring rate of 800 rpm using propeller stirred for 5h at room temperature to remove the solvent completely by evaporation. The mineral oil is decanted and microparticles collected by vacuum filtration were washed thrice with n-hexane and dried at room temperature for 24 h. (Bolourtchian *et al.,* 2005).

Table: 1: Formulations of ORST Inner core Tablet.

Ingredients	OGC-1 (%)	OGC-2 (%)	OGC-3 (%)	OGC-4 (%)	OGC-5 (%)	OGC-6 (%)
ORST-βCD [1:2M]	70	70	70	---	---	---
ORST-SD Mannitol[1:3]	---	---	---	70	70	70
Ludiflash	18.5	14	11	18.5	14	11
Kollidon CLF	---	4.5	7.5	---	4.5	7.5
Kollidon-30	04	04	04	04	04	04
SLS	02	02	02	02	02	02
Sucralose	02	02	02	02	02	02
Cherry Flavour	01	01	01	01	01	01
Methyl Paraben	0.5	0.5	0.5	0.5	0.5	0.5
Talc	01	01	01	01	01	01
Mg.stearate	01	01	01	01	01	01
Titanium dioxide (Red)	q.s	q.s	q.s	q.s	q.s	q.s

***** OGC–Formulations of Inner Core Tablet contain 60mg of ORST.

Table: 2 Formulations of VLFXN Outer coat layers

Ingredients	VLF-1 (%)	VLF-2 (%)	VLF-3 (%)	VLF-4 (%)	VLF-5 (%)	VLF-6 (%)
VLFXN+βCD [1:3M]	45	45	45	---	----	----
VLFXN +Eudragit EPO [1:3]	----	----	----	55	55	55
Ludipress LCE	43	23	23	33	17	17
Maltodextrin	---	20	---	----	16	---
Xanthan Gum	---	----	20	----	----	16
Kollidon-30	02	02	02	02	02	02
Citric acid	02	02	02	02	02	02
Sucralose	02	02	02	02	02	02
Peppermint Flavour	02	02	02	02	02	02
Propyl Paraben	0.5	0.5	0.5	0.5	0.5	0.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5
Mg.stearate	02	02	02	02	02	02

Formulation and Preparation of Press-Coated Tablet-In-Tablets

Formulation of dispersible core tablets by direct compression

The rapid disintegrating inner core tablets were prepared by the direct compression method taking the required quantity of the ORST-β-CD complex or ORST solid dispersion and the excipients as shown in (Table no. 01). And passed through a 44 mesh and were mixed for 20 minutes, followed by addition of talc and magnesium stearate.

The mixture was again blended for 10 minutes and 200mg of the resultant powder was manually compressed in Karnavathi-Rimek Minipress II DL, using 9mm round punches to get the core tablet.

Formulation of mixed blend for outer layers

The outer layers blend was prepared by direct mixing method taking the required quantity of the VLFXN microspheres or VLFXN-β-CD complex and the excipients as given in the (Table 02.) And passed through a 44 mesh sieve and dry mixed for about 10 minutes, followed by addition of lubricants, talc and magnesium stearate. The mixture was again blended for 10 minutes and used as press-coating powder.

Preparation of press-coated tablet-in-tablets

First the 400 mg of lower outer layer powder was weighed and placed as the lower layer in the 14mm round concave punches die cavity. Then the core tablet of ORST weighing 200mg was placed at the centre and pre-compression was done on a Karnavathi-Rimek Minipress II DL bilayer compression machine. Then the upper outer layer of 400mg of coating material was weighed and added manually onto a pre-compressed layer in the die cavity.

Final compression was done at an optimum pressure to obtain a neat shiny press coated tablet-in-tablet of ORST and VLFXN shown in (Fig. no.01).

Fig. 1: Chewable Press coated tablet-in-tablet of ORST Inner core and VLFXN Outer layers.

EVALUATIONS

Solubility determination of ORST

Solubility study of ORST in distilled water was carried out as per the standard shake flask method. Excess amount of the drug was added to the 10ml of water in a 25ml conical flask with a closure, and the resulting mixture was shaken at room temperature on a rotary shaker (Remi) at 100 rpm for 24h. The solution was filtered using a whatman filter paper of 0.45µ and the filtrated solution after suitable dilution was assayed by HPLC.

Evaluation of compressed tablets

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (ER-182-A), and the test was performed according to the official method described in IP.

Drug Content

Five tablets from each formulation were weighed, and the drug was extracted in suitable solvent. The drug content was determined following the methods described in the IP and USP.

Hardness and Friability

For each formulation, the hardness and friability of six tablets were determined as per the methods described in the IP, using the Pfizer Hardness tester (Toshiba India, New Delhi) and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively.

In vitro disintegration pattern study of core tablets

The in vitro disintegration pattern of core tablets was studied as per method described by (Chaudhari S. P.*et al*. 2007) with slight modification. Disintegrating pattern was studied visually by taking images of the core tablets in a petri dish containing 10ml of distilled water at the specified time intervals 0.5min, 1min, 1.5min and 2mins.

In vitro drug release study of tablet-in-tablets

In-vitro dissolution studies of core tablets and press coated tablets were performed in a USP II paddle apparatus at 37 ± 0.5 °C with 75 rpm.

Dissolution medium was 3% w/v aqueous solution sodium lauryl sulfate with 0.5% of sodium chloride, adjusted to pH6 with phosphoric acid. Five ml of filtered solution was withdrawn manually using syringe disc filter, at the specified time intervals and 5 ml of fresh dissolution medium was replaced. The collected liquid samples were filtered again with 0.45µ whatman filter paper and the filtrate after suitable dilution was assayed by HPLC (Taylor *et al.*, 2010).

Taste evaluation of chewable press coated tablet-in-tablets

Taste panel consisting of five volunteers evaluated the taste of optimized formulation chewable tablet-in-tablets. The chewable tablets were kept for five minutes, over the tongue and chewed in the mouth while applying some pressure by the tongue and then disgorged completely and rinsed out with water. The taste, after-taste sensation and other effects were evaluated on a scale of 1±5 (Cohen *et al.*, 2009).

RESULTS AND DISCUSSION

The developed formulation was designed to enhance the solubility of ORST and mask the bitter taste of VLFXN and prepare a chewable press coated, tablet-in-tablet. A reverse phase HPLC method was developed for the simultaneous estimation of ORST and VLFXN in the formulation. The retention time for VLFXN and ORST was 5.5 minutes and 9 minutes respectively (Fig. no.02).

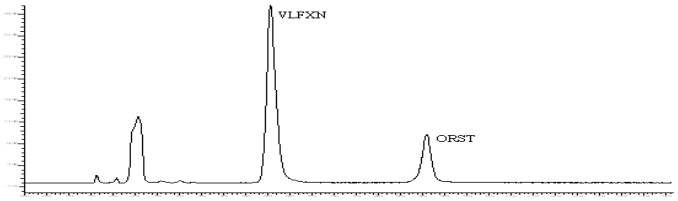

Fig. 2: HPLC Chromatograph of ORST and VLFXN .

In the solubility enhancement of ORST compared to solid dispersion of ORST-mannitol and ORST-βCD (PM) in different ratios, ORST-βCD complex in the ratio of [1:2M] was found to increase the solubility from 1.8± 0.16 mg/ml to 8.9± 0.24 mg/ml (Fig. no. 03).

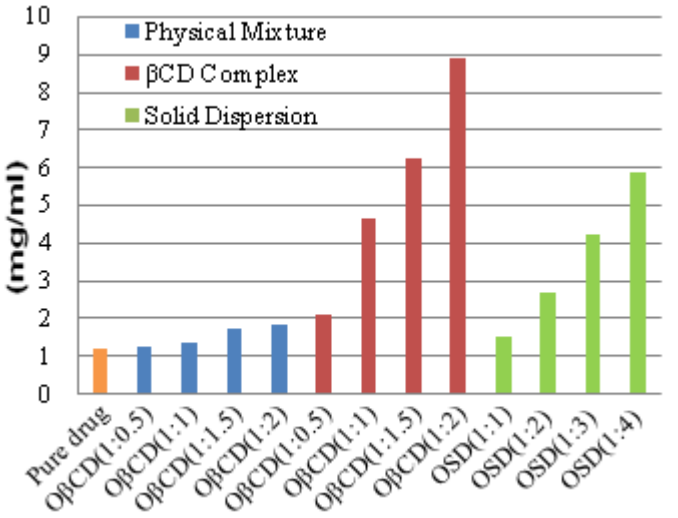

Fig. 3: Solubility of ORST-Pure, ORST-βCD (PM), ORST-βCD-Complex and Solid dispersions.

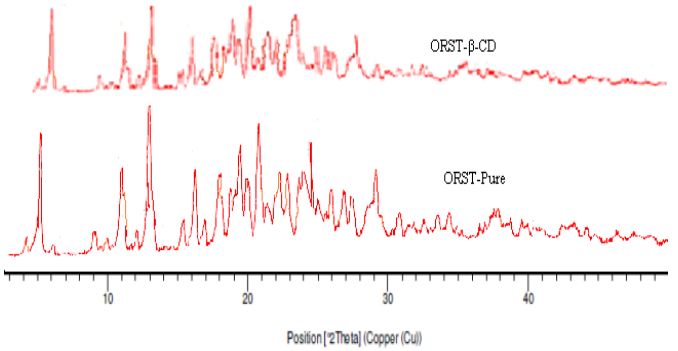

Fig. 4: X-ray Diffractograms of (a) ORST Pure (b) ORST-β-CD (1:2) complex.

And it was less bulky to prepare the inner core tablet weighing 200mg. The ORST-βCD complex was characterized by XRD analysis there was no change in the spectrum, which indicate the drug crystalline state was intact (Fig. no.04). In case of masking the bitter taste of VLFX, compared to VLFXN- β-CD

complexes, microparticles of VLFXN with Eudragit EPO in the ratio of [1:3] was found to be more effective. The characterization of VLFXN microspheres was done by SEM (Fig. no. 05).

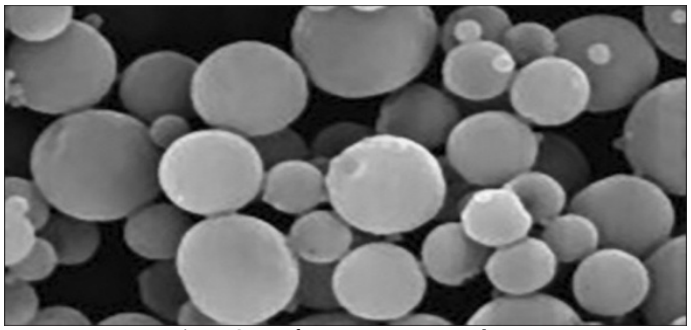

Fig. 5: SEM of VLFXN Microparticles.

The microparticles were spherical in shape and the size range of 200-400µ. In the preformulation study, the selected excipients compatibility with the drugs was analysed by FTIR spectroscopy. No drug and excipients interaction was found by the FTIR Spectrum (Fig. no. 06 & 07).

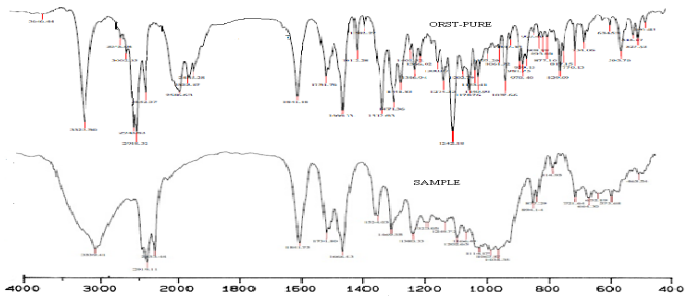

Fig. 6: IR Spectra of ORST Pure and with Excipients (OGC-2).

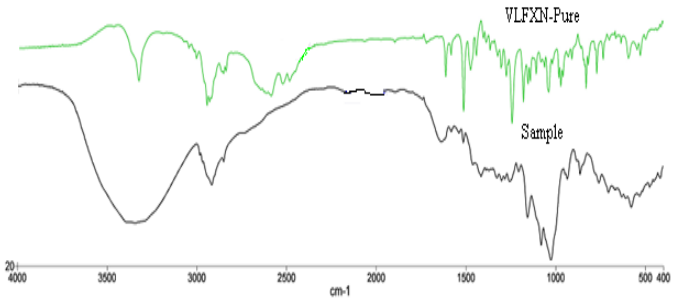

Fig. 7: IR Spectra of Pure VLFXN and with Excipients (VLF-5).

To obtain the optimised formulation of ORST and VLFXN chewable tablet-in-tablet, six formulation trials of core tablet were done and the results obtained are shown in the (Table no.03) and (Fig. no.08 and 09).

From the results obtained (OGC-2) formulation was chosen as optimised core tablet formulation as it was found to disintegrating within two minutes and releasing the 90% of drug in 10mins. The possible reason could be the preparation of ORST-βCD complex and incorporation of ludiflash as co-processed excipient in the formulation. In a study conducted by (Late and Banga 2010), β-cyclodextrin was used as excipient in the concentration of 30-60% was found to reduce the wetting time and enhance the disintegration. And in a comparative study of novel ODT co-processed excipients conducted by (Stoltenberg *et al.*, 2011), the tablets prepared using ludiflash were of good friability and hardness and release the drug rapidly in comparison to the other co-processed excipients.

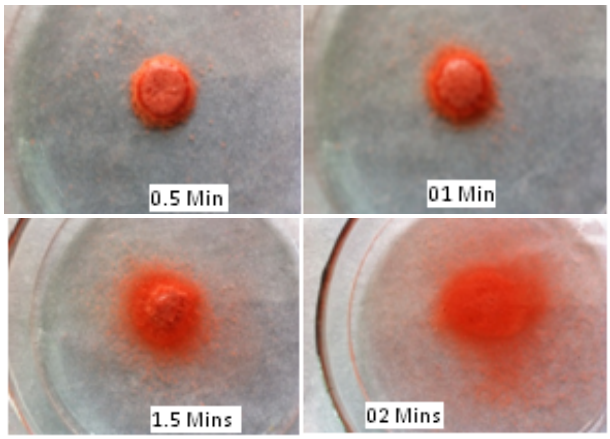

Fig. 8: Disintegrating Pattern of ORST Inner core Optimized formulation (OGC-2) .

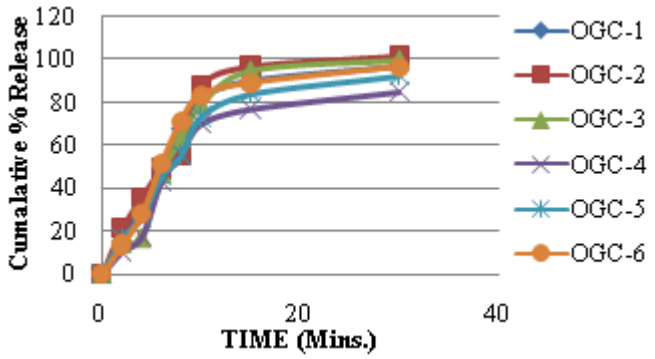

Fig. 9: Drug Release Profile of Six Formulations of ORST Inner core (OGC 1-6)

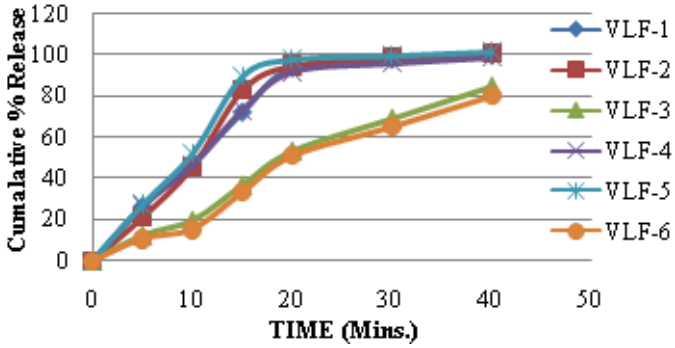

Fig. 10: Drug Release Profile of Six Formulations of VLFXN Outer coat layers (VLF 1-6)

Further, taking a placebo core tablet, six formulation trials of coating layers were tried. The results of all the six tablet-in-tablet formulations are shown in the (Table no.04) and (Fig. no.10). On the basis of results obtained (VNF-5) formulation was

selected as the outer coat layer optimised formulation. Then, taking (OGC-2) inner core and (VNF-5) outer layer, the optimized formulation of press coated tablet-in-tablets (OPTT) were compressed. The physico-chemical evaluation results of (OPTT) formulation were found to be within the standard limits and are shown in the (Table no.05). The overall palatability is a critical factor in the development of the chewable dosage form and Eudragit EPO in appropriate ratio as microspheres or complex can mask the bitter taste of a drug (Yan YD *et al.*, 2010 and Nakano Y *et al.*, 2013).The optimized formulation taste was evaluated by the taste panel consisting of five volunteers, from whom informed consent was obtained. The volunteers rated the (OPTT) formulation as an average and agreeable with the statistically acceptable p value of <0.05 between the individuals, as shown in (Fig. no.11). This indicates that the VLFXN microparticles prepared with Eudragit EPO in the ratio of [1:3] has significantly masked the bitter taste of the drug. Finally, the in-vitro dissolution study of the optimized (OPTT) was carried out and a lag time of five minutes was observed in the release of ORST form the (OPTT) formulation. This could be due to the covering of VLFXN outer layers. In a study of press coating of immediate release powders onto a controlled release core tablets, carried out by the (Kenneth C *et al.*, 2003), noted that a lag time can be reduced or eliminated by adding appropriate quantity of core tablet drug to the coating layers. However, the release of both drugs ORST and VLFXN at the end of 15mins was found to be 86 % and 92% respectively as shown in (Fig. no.12). Further in-vivo clinical studies in healthy human volunteers are being planned to investigate the PK/PD parameters of the developed press coated tablet-in-tablets.

Table: 3: Properties of the ORST Core Tablet Formulations

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Content Uniformity (%)
OGC-1	200.9±1.78	3.1±0.51	3.3±0.08	0.95±0.046	98.7±0.52
OGC-2	200.3±1.35	3.3±0.64	3.2±0.06	0.92±0.022	101.8±0.32
OGC-3	200.9±1.12	3.5±0.41	3.2±0.02	0.96±0.058	100.3±0.21
OGC-4	199.7±1.54	3.4±0.53	3.3±0.04	0.97±0.078	98.7±0.80
OGC-5	202.1±1.62	3.6±0.31	3.1±0.08	0.95±0.046	99.5±0.69
OGC-6	201.8±1.71	3.7±0.89	3.0±0.05	0.98±0.019	98.3±0.34

All values are expressed as mean ± SD, n=3

Table: 4: Properties of the Tablet-in-Tablet Formulations.

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Outer layers- VLFXN Content Uniformity (%)
TTF1	1001.3±1.96	5.6±0.14	5.5±0.012	0.097±0.09	99.7±0.64
TTF2	998.8±1.90	5.5±0.13	5.7±0.014	0.098±0.05	103.8±0.20
TTF3	1000.9±1.87	5.9±0.14	5.2±0.013	0.082±0.06	100.6±0.31
TTF4	1000.9±1.90	5.5±0.15	5.6±0.012	0.098±0.08	102.6±0.48
TTF5	1001.3±1.96	5.7±0.14	5.5±0.014	0.091±0.09	103.8±0.20
TTF6	999.7±1.97	5.4±0.12	5.6±0.011	0.099±0.06	102.3±0.34

All values are expressed as mean ± SD, n=3

Table: 5: Properties of the optimized Tablet-in-Tablet (OPTT); OGC-2 Inner core and VLF-5 Outer layers\

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	ORST-Core Tablet Content Uniformity (%)	VLFXN-Outer layers Content Uniformity (%)
OPTT	1001.4±1.93	5.7±0.16	5.6±0.016	0.097±0.08	99.7±0.65	102.7±0.23

All values are expressed as mean ± SD, n=3

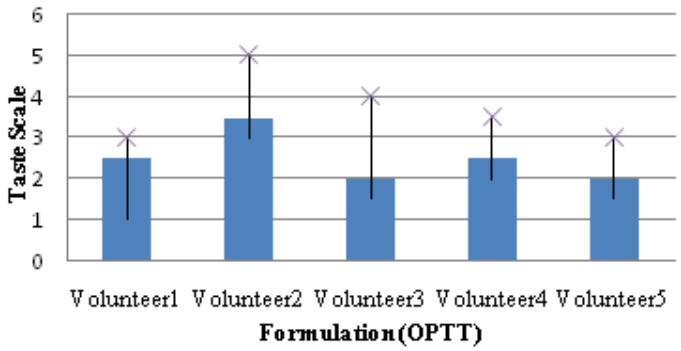

Fig. 11: Taste Evaluation of Optimized Formulation (OPTT), on a scale of five.

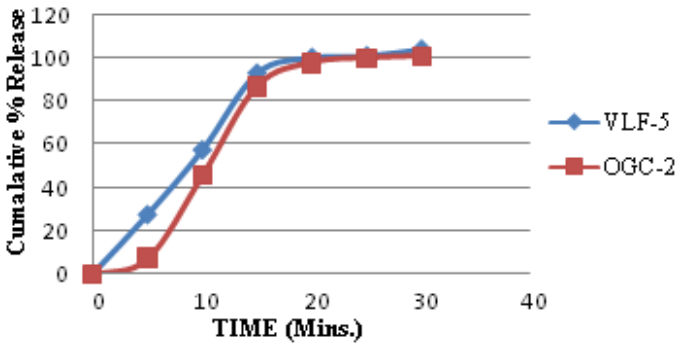

Fig. 12: Drug Release Profile of Optimized Tablet-in-Tablet Formulation (OPTT); OGC-2 Core press coated with VLF-5 Outer layers

CONCLUSION

People who are excessive obese are at increased risk of becoming depressed, and are prone to have binge eating disorder. Hence, the developed chewable press coated tablet-in-tablet of ORST and VLFXN can be excellent drug delivery system for treating patients with obesity and BED as it is palatable and can be chewed conveniently without water. However, further in-vivo clinical studies are recommended to ensure the safety and efficacy of the dosage form.

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