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FORMULATION AND EVALUATION OF ORLISTAT FAST DISSOLVING TABLETS

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ABSTRACT

The objective of the study was to formulate and evaluate orally disintegrating tablet of orlistat. Direct compression method was used to formulate orally disintegrating tablet of orlistat by employing different superdisintegrants, polymers, and magnesium stearate (lubricant), Talc. These prepared formulations were then evaluated. Dissolution and drug content tests were performed using USP apparatus II and ultraviolet spectrophotometry, respectively. All formulations showed compliance with pharmacopeia standards. The effect of superdisintegrants concentration and direct compression method on drug release profile was studied. Release profile of F3 were found to be satisfactory comparing to other formulations. F3 Formulation as processed excipient was found to be the best superdisintegrants for the preparation of orlistat orally disintegrating tablets formulations. Due to it has exhibited faster disintegration time and best dissolution profile when compared to other formulations.

KEYWORDS: Orlistat, superdisintegrants, natural and synthetic polymers, direct compression technique, in-vitro drug release studies.

1. INTRODUCTION

A fast dissolving system can be defined as a dosage form for oral administration, which when placed in mouth, rapidly dispersed or dissolved and can be swallowed in form of liquid. Recently fast dissolving formulation is popular as NDDS because they are easy to administer and lead to better patient compliance.[1,2] Pediatric and geriatric patient have difficulty in

swallowing the conventional dosage forms. Fast dissolving and fast dispersing drug delivery system may offer a solution to these problems. Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy.[3] Fastdisintegrating tablets are gaining prominence as new drug-delivery systems. These dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing. Orlistat reduces the LDL concentration in the blood by inhibiting gastric and pancreatic lipases (the enzymes that break down triglycerides in the intestine).[4,5] The primary effect of orlistat is local lipase inhibition within the GI tract after an oral dose. When lipase activity is blocked, triglycerides from the diet are not hydrolyzed into absorbable free fatty acids and are excreted undigested instead, thereby reducing caloric intake.[6] A single dose of orlistat will prevent approximately 30% of dietary fat from being absorbed, which indicates its effectiveness in controlling dyslipidemia. It also exhibits antiproliferative and antitumor properties in prostate and breast tissues.[7]

2. MATERIALS AND METHOD

MATERIALS

Orlistat was collected as a gift sample from Hetero labs, Hyderabad, and polymers such as Sodium alginate, HPMC, Ethylcellulose, eudragit and other materials like Calcium chloride, methanol were purchased from AR chemicals.

METHODOLOGY[8,9,10]

Drug excipient compatability

The pure OST (drug) and its physical mixture were subjected to IR spectral studies by employing the KBr pellet method using FTIR spectrophotometer. One to two milligram of fine solid powder of OST and 200-300 mg of dry powder of KBr (IR grade) were taken in a mortar and mixed well with the help of the spatula. Spectrum measurement was carried out using KBr disk method in the wavelength region of 4000-400 cm^{-1} by FTIR spectrophotometer. The spectra obtained for OST, and the physical mixture was compared.

Formulations Table.

Table 1: Formulation of core tablets of Orlistat.

Ingredients(mg)	F1	F2	F3	F4	F5
Drug	200	200	200	200	200
HPMC	50	-	-	25	
Sodium alginate	-	50	-	25	25
Ethylcellulose			50	-	25
Sodiumstarch glycolate	10	10	10	10	10
Talc	2	2	2	2	2
Magnesium Stearate	3	3	3	3	3
MCC	35	35	35	35	35
Total wt	300	300	300	300	300

Preparation method

Preparation of tablets by Direct compression method

Different matrix embedded formulations of Orlistat were prepared by direct compression method using varying proportion of polymers either alone or in combination. The ingredients were passed through a 60 mesh sieve. Calculated amount of the drug, Various polymers, Super disintegrant agent and filler (MCC) was mixed thoroughly. Magnesium stearate was added as lubricant; the appropriate amount of the mixture was weighed and then compressed using a an Ten station rotary press at a constant compression force equipped with a 8-mm flat-faced punches at a compression force required to produce tablets of about 7–8 kg/cm^2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Evaluation studies[11,12,13]

i) Pre compression parameters

a) Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation.

Bulk density = weight of sample taken /volume noted

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the cylinder was dropped at 2-second intervals onto a hard wooden surface three times, from a height of one inch. The volume was recorded and the bulk density was calculated.

b) Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the surface was carefully smoothed and the volume was measured. Tap density was calculated by measuring final volume (V_f) after 50 taps on wooden surface from 6 inch height and was expressed in g/cm^3.

Bulk density = W/V_o

Tapped density = W/V_f

c**) Compressibility index**

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

The compressibility index and Hausner ratio may be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) as follows:

$$\text{Compressibility index} = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} X\ 100$$

$$\text{Hausner ratio} = \frac{\rho_{tapped}}{\rho_{bulk}}$$

d) Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\theta = h/r$

ii) Post compression parameters

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage and none deviate by more than twice the percentage shown.

Thickness

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$\% F = \{1-(Wo/W)\} \times 100$

Content Uniformity

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Orlistat. Dissolve the weighed quantity of powder into 100 ml of phosphate buffer (pH 6.8) solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask

and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at 207nm using reagent blank.

Disintegration time

The in vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus, and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Wetting time

Wetting time is closely related to the inner structure of the tablets and the hydrophilicity of the excipient. The time required for water to reach the upper surface of the tablet is noted as the wetting time. A piece of tissue paper folded double was placed in a Petri plate (internal diameter of 6.5 cm) containing 6 ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured.

The weight of the tablet before keeping in Petri dish was noted (W_b) using Shimadzu digital balance. The wetted tablet from the Petri dish was taken and re weighed (W_a) using the same. The Water absorption ratio, R, was determined according to the following equation:

$$R = \frac{Wa - Wb}{Wb} \times 100$$

***In- Vitro* Release study**

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 period of time. Temperature maintained at 37±5.The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, and make the volume with buffer. The diluted samples were assayed at 207 nm against reagent blank.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared tablets

of Orlistat were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 30 days.

3. RESULTS AND DISCUSSION

FT-IR Spectrum of Orlistat

FT-IR Spectra of Orlistat and F3 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Orlistat and polymer. It also confirmed that the stability of drug during microencapsulation process.

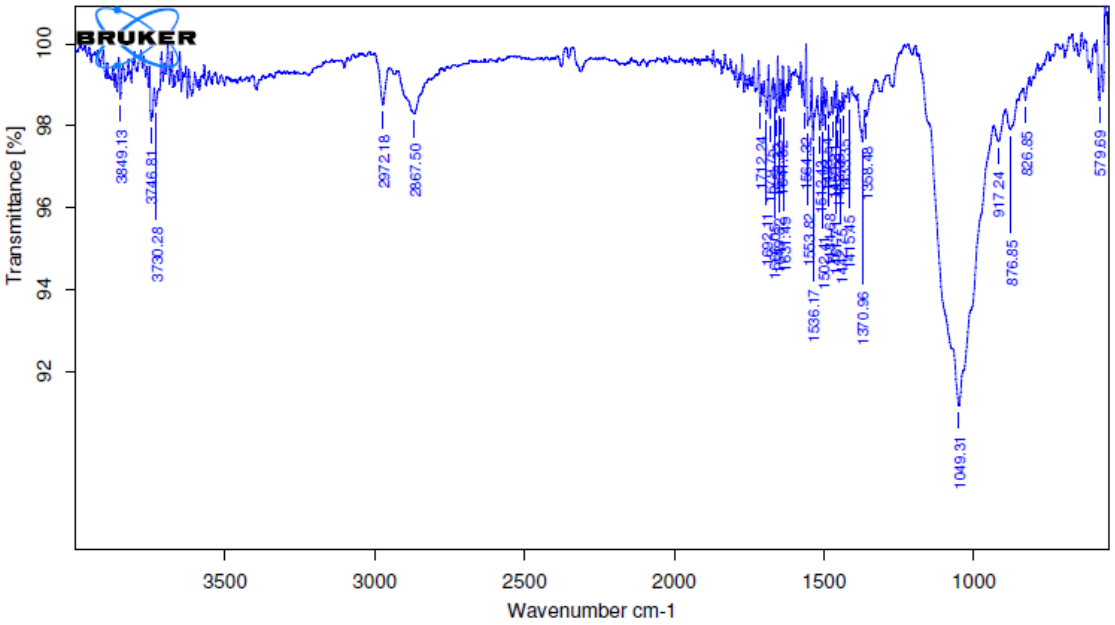

Fig-1: FTIR Studies of Orlistat.

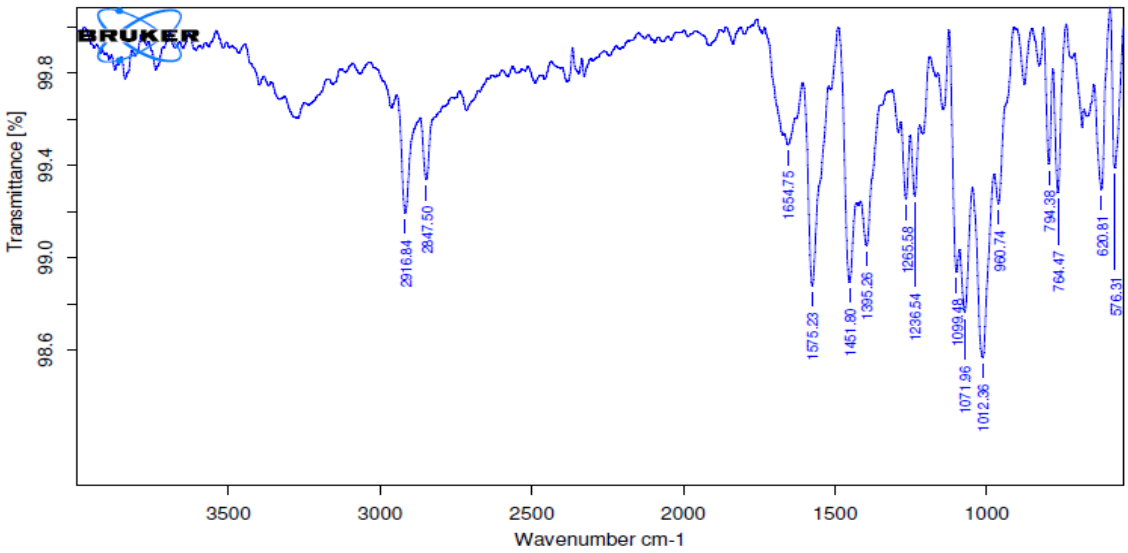

Fig 2: FTIR Studies of optimized formulation.

Evaluation studies

Pre compression parameters

a) **Bulk Density:** The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.431-0.471

b) **Tapped density:** The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.515-0.563.

c) **Angle of repose:** The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 29 to31^0

d) **Compressibility index:** Compressibility index was carried out, it found between 10% to 22.58% indicating the powder blend have the required flow property for compression.

Characterization of Formulation

Table-2: Pre compression parameters of Orlistat fast dissolving tablets.

F. No	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose(0)
F1	0.431	0.522	17.43	1.21	29^0c
F2	0.471	0.563	16.34	1.19	29^0c
F3	0.463	0.524	11.64	1.13	30^0c
F4	0.455	0.515	11.65	1.13	30^0c
F5	0.462	0.531	12.99	1.14	31^0c

Post compression parameters

Weight variation

All the formulated (F1 to F5) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness

Tablets mean thickness (n=3) were uniform in F1 to F5 formulations and were found to be in the range of 2.3 mm to 2.6 mm.

Hardness

The measured hardness of tablets of each batch ranged between 3.24 to 3.46 kg/cm^2. This ensures good handling characteristics of all batches.

Friability

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity

The percentage of drug content for F1 to F5 was found to be between 95.20% and 98.55% of Orlistat, it complies with official specifications.

Disintegration Time

In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods. The shortest registered disintegration time was 45 sec, while the longest greatly exceeded 54 sec.

Wetting Time

The weight of the tablet before keeping in Petri dish was noted (W_b) using Shimadzu digital balance. The wetted tablet from the Petri dish was taken and re weighed (W_a) using the same. The shortest registered wetting time was 1.25 s, while the longest greatly exceeded 1.52 sec.

Table 3: Evaluation parameters of orlistat fast dissolving tablets.

F. No.	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drug content (%)	Disintegration time(sec)	Wetting time (sec)
F1	299	2.3	3.24	0.52	96.10	54	125
F2	298	2.4	3.26	0.45	95.20	53	134
F3	300	2.6	3.28	0.54	98.55	51	155
F4	297	2.4	3.46	0.51	97.50	49	152
F5	300	2.5	3.40	0.53	96.58	45	128

DISSOLUTION STUDIES

All the three formulation of Orlistat fast dissolving tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table 4: Dissolution Profile of batch no. F1 to F5.

%Drug Release					
Time	**F1**	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
2	25.36	26.39	25.98	24.59	26.79
4	35.26	36.29	37.59	39.65	34.56
6	50.26	49.67	50.26	49.99	48.26
8	62.35	59.66	61.29	64.26	63.54
10	70.26	70.98	71.29	73.29	72.59
15	79.36	81.26	82.29	83.96	83.85
20	86.26	87.26	88.99	90.26	89.56
30	93.26	95.35	97.68	93.48	94.56

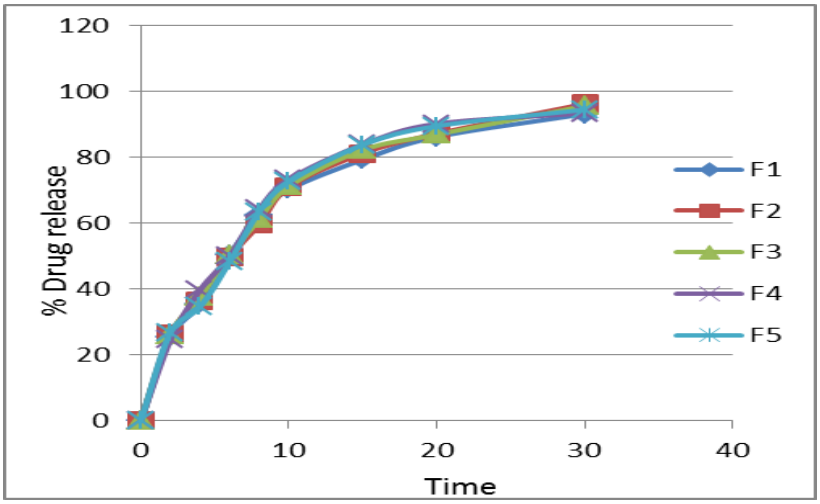

Fig-3: Percentage drug release of all formulations.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 30 days. Parameters quantified at various time intervals were shown.

Table 5: Stability studies of all formulations.

Formulation Code	Parameters	Initial	1st Month	Limits as per Specifications
F-3	25^0C/60%RH % Release	97.68	97.52	Not less than 85 %
F-3	30^0C/75% RH % Release	97.68	97.60	Not less than 85 %
F-3	40^0C/75% RH % Release	97.68	97.61	Not less than 85 %

4. CONCLUSION

The aim of the present study was to develop an optimized formula for fast dissolving tablet containing orlistat. Orlistat is used to aid in weight loss, or to help reduce the risk of regaining weight already lost. This medicine must be used together with a reduced-calorie diet. After pre-formulation studies it was decided to prepare fast dissolving tablets prepared by direct compression method. In the formulation of sodium starch glycolate, were used as super disintegrants. Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The compressed bilayer tablets were also evaluated for weight variation, hardness, friability, drug content, disintegration time and in vitro drug release. In the above studies F3 formulation showed promising results. It was further supported by FTIR analysis which showed that F3 had no interaction with excipients. The stability studies were carried out for the optimized batch F3 for 30days and it showed acceptable results. So F3 formulation was considered as the optimized formulation.

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