ORIGINAL ARTICLE

Formulation Design and *in vitro* Evaluation of Orodispersible Tablets of Orlistat by Direct Compression Method

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Abstract

Objective: The objective of the study was to formulate and evaluate orally disintegrating tablet of orlistat. **Materials and Methods:** Direct compression method was used to formulate orally disintegrating tablet of orlistat by employing different superdisintegrants, entragit, and magnesium stearate (lubricant), Talc. These prepared formulations were then evaluated using pharmacopeia and non-pharmacopeia methods. Dissolution and assay tests were performed using USP apparatus II and ultraviolet spectrophotometry, respectively. **Results:** All formulations showed compliance with pharmacopeial standards. The effect of superdisintegrants concentration and direct compression method on drug release profile was studied. Release profile of F12 which contains 2% of Ac-di-sol in combination with entragit, were found to be satisfactory comparing to other formulations. **Conclusion:** Formulation prepared with Ac-di-sol in combination with entragit (F12), 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.

Key words: Disintegration, evaluation, formulation, orlistat

INTRODUCTION

Today most of the pharma companies are focusing on solid oral drug delivery systems that offer greater patient compliance and effective dosage. Oral route is undoubtedly the most important drug delivery route which offers various advantages like convenience of self-administration and easy manufacturing along with saving costs.[1-3]

However many patients, especially geriatrics have dysphagia or difficulty in swallowing tablets and hard gelatin capsules and skip their prescribed medication, thus resulting in improper treatment. In these cases, orally disintegrating tablets (ODTs) have been found to be greatly useful. Thus, most geriatric patients prefer ODTs. Water plays an important role in the absorbing of oral dosage forms. Patient might find it difficult in cases where there is no availability of water for oral administration.[4,5] To achieve these medical needs, pharmacists have developed novel oral dosage form known as ODTs.[6-8] According to European Pharmacopeia the term "Orodispersible tablet" is defined as uncovered tablet for buccal cavity, where it dissolves before swallowing.[9]

In the past several years advanced new technologies were developed for the manufacture of orodispersible tablets with remarkable features, such as extremely low disintegration time, pleasant mouth feel, and sugar-free tablets.[2,10] The methods applied for manufacture of orodispersible tablets include direct compression molding and lyophilization cotton candy process, nanonization,[11-16] and quick dissolve film formation.[16] Most of the technologies require specialized processing conditions and equipment's except for some conventional cost-effective

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technologies such as direct compression and disintegration. To speed up the manufacturing process and reduce the costs of production direct compression method is employed, while a major requirement for direct compression process is a selection of excipients.

However numerous literature reports suggest the use of relatively expensive semi-synthetic polymeric superdisintegrants is essential in the development of ODTs. Example of these are; crospovidone,[17,18] croscarmellose sodium (carboxymethyl cellulose),[18] and sodium starch glycolate (Primojel®, Explode®),[19] are added to the formulation to achieve rapid disintegration when it is placed on the tongue, accompanied with good mouth feel.

Orlistat, also known as tetrahydrolipstatin, is intended to treat obesity. Chemically orlistat is a [(1S)-1-[(2S, 3S)-3-hexyl-4-oxo-oxetan -2-y1] methyl] dodecyl] (2S)-2-formamido-4-methyl-pentonate. It acts by reducing the low-density lipoproteins concentration in the blood by inhibiting gastric and pancreatic lipases. The primary effect of orlistat is local lipase inhibition within the gastrointestinal tract after an oral dose.[20,21] A single dose of orlistat will prevent approximately 30% of dietary fat from being absorbed.[22] Orlistat is an important drug in the prophylactic management of obesity and for the management of type-2 diabetes. In this paper, we report the formulation and evaluation of orally disintegrating tablet of orlistat.

MATERIALS AND METHODS

Materials

All ingredients used in this research were commercial samples. Active agent Orlistat (Dr. Reddy's Lab. Hyd., India) Sodium starch glycolate, Crospovidone, Croscarmellose sodium (Ac-Di-Sol), microcrystalline cellulose, mannitol magnesium stearate and talc, (standard deviation [SD]. Fine, Mumbai) as a gift samples. Pharmatose and pearlitol flash, (Nectar Life Sciences, Hyd. India) Entragit (Sri Nihal traders, Hyd.) and Sodium stearyl fumarate (Dr. Reddy's, Hyd.). All the chemicals used are of analytical grade.

Instruments

Electronic single pan balance (Riddhi, Ahmedabad), tapped density (Dt) apparatus, pH meter (Kshitij innovations, Ambala cantt) Disintegration test apparatus (Electrolab, Ahmedabad.), Roche Friabilator (Pharmalab, Ahmedabad), dissolution test apparatus (Electrolab), ultraviolet (UV) visible spectrophotometer (analytical technologies), Mesh#21,32 (Sethi), digital screw gauge (Mitutoyo, Japan.), Monsanto Hardness tester (Pharmalab, Ahmedabad.), Tablet punching machine included with 8 stations (Riddhi, Ahmedabad.), and Hot air oven from Bio-Tech India.

Formulation development

Orlistat dispersible tablets were prepared according to the formula given in Table 1. A total number of 13 formulations were prepared by direct compression method. All the ingredients, including drug, were weighed accurately and passed through 60 mesh sieve separately and collected. The ingredients were weighed and mixed in a geometrical order. The active ingredient and disintegrating agents were weighed and mixed in a small portion of both each time and screen the damp mass into granules and allowed to kept side for drying the blended powder. After the powder dried, allowed to pass through a screen of smaller size. A dry lubricant is added to the powder by blending with the powder. It reduces the friction between the tablet and the walls of the die cavity. Last step in which the tablet is fed into the die cavity and compressed between a lower and an upper punch. 10 mm size punches were used for punching tablets. The tablets were packed in aluminum foil and stored at room temperature.

Preparation of standard curve of orlistat

The UV scanning of drug sample was carried out using a solution of drug dissolved in 3% sodium lauryl sulfate (SLS) buffer solutions at a concentration of 100 µg/ml. The λmax was observed at 254 nm. The calibration curve of orlistat was obtained by dissolving the drug in buffer solutions, and absorbance was measured at 254 nm buffer solution used as a blank.

Method of preparation of 3% SLS buffer solution

Weight accurately about 3 g of SLS and dissolve in 100 ml of distilled water. To it add 0.5% of NaCl (anti-foaming agent). Accurately weighed quantity of orlistat (100 mg) was dissolved in 3% SLS buffer solution, and the volume made up to 100 ml with the same.

S.S I⇒1000 µg/ml.

About 10 ml of stock solution I was further diluted with 100 ml of 3% SLS buffer to get a working standard S.S I⇒100 µg/ml. Again 10 ml of above solution was further diluted with the same to get a concentration of 10 µg/ml. Then, aliquots of 1-6 mcg/ml of stock solution was pipetted into 10 ml volumetric flask and diluted up to the volume with buffer. The absorbance was measured at 254 nm against a blank (3% SLS buffer).

Evaluation parameter (pre-compression parameters)

Bulk density (D_b)

It is the ratio of the total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder

Table 1: Formula for orlistat tablet formulation

Ingredients (mg)	F1 10%	F2 10%	F3 8%	F4 12%	F5 6%	F6 8%	F7 8%	F8 8%	F9 2%	F10 3%	F11 2%	F12 2%	F13 3%
Orlistat	60	60	60	60	60	60	60	60	60	60	60	60	60
Mannitol	117	-	121	113	125	121	121	121	129	125	-	-	125
Pharmatose	-	117	-	-	-	-	-	-	-	-	-	-	-
Entragit	-	-	-	-	-	-	-	-	-	-	133	133	-
Ac-di-sol	20	20	16	24	12	-	-	-	4	6	-	4	6
Crospovidone	-	-	-	-	-	16	-	-	-	-	-	-	-
MCC 101	-	-	-	-	-	-	16	-	-	-	4	-	-
SSG	-	-	-	-	-	-	-	16	-	-	-	-	-
Pearlitol flash	-	-	-	-	-	-	-	-	4	6	-	-	6
SSF	2	2	2	2	2	2	2	2	2	2	2	2	-
Magnesium stearate	0	0	0	0	0	0	0	0	0	0	0	0	2
Talc	1	1	1	1	1	1	1	1	1	1	1	1	1
Tablet weight	200	200	200	200	200	200	200	200	200	200	200	200	200

into a measuring cylinder, and the volume was noted. It is expressed in g/ml and is given by,

$$D_b = \frac{M}{V_0}$$

Where, M is the mass of powder, V0 is the bulk volume of the powder

Tapped Density (D_T)

It is the ratio of the total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by,

$$D_T = \frac{M}{V_1}$$

Where, M is the mass of powder, VT is the tapped volume of the powder.

Hausner ratio

Hausner's ratio is the ratio of tapped density to bulk density

$$\text{Hausner ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

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 measured 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.

$\theta = \tan{-1}\ (h/r)$

Where,
θ is the angle of repose
h is the height in cm
r is the radius in cm.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of the powder formed.

Carr's index (I)

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Post compression parameters.

Hardness

The hardness of a tablet is indicative of its tensile strength and is measured in terms of load/pressure required to crush it when placed on its edge. A number of handy hardness testers such as Mosanto or Pfizer type are currently in use, and it is expressed in Kg/cm^2. The hardness is a function of physical properties of granules like their hardness and deformation under load, binders and above all the compressional force. The hardness has an influence on disintegration and dissolution times and is such a factor that may affect bioavailabilities.

Hardness of about 5 kg is considered to be minimum for uncoated tablets for mechanical stability.

Friability (F)

In general, it refers to the loss in weight of tablets in the containers due to removal of fine particles from their surfaces. However, in wider sense chipping and fragmentations can also be included in friability. Friability, generally, reflects poor cohesion of tablet ingredients. Standard devices have been fabricated to measure friability. The friability of the tablet was determined using Roche Friabilator' consist of a circular plastic chamber, divided into 2-3 compartments. It is expressed in percentage (%). 10 tablets were initially weighed (Winitial) and transferred into the Friabilator. The Friabilator was operated at 25 rpm for 4 min. The tablets were weighed again (Wfinal). The percentage friability was then calculated.

Weight variation

About 10 tablets were selected randomly from the lot and weighed individually to check for weight variation. Indian pharmacopeia limit for weight variation in case of tablets weighing more than 150 mg is ±7.5%.

Thickness

The thickness of the tablets was measured by screw gauge. It is expressed in mm.

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.

Content uniformity test

The powder equivalent to 60 mg of orlistat was dissolved in 10 mL of 3% SLS solution and volume was adjusted to 100 mL with the same buffer. From this solution, 1 mL was taken and made up to 100 mL using the same solution, and the solution was analyzed at 254 nm by UV-visible spectrophotometer using the buffer as the blank. The drug content was calculated using the standard calibration curve.

In vitro dissolution studies

In vitro dissolution studies for all the formulated tablets of orlistat were conducted using USP Type II paddle method at 50 rpm in 900 mL of 3% (SLS) solution as the dissolution medium. The dissolution medium was maintained at 37 ± 0.5°C 0.10 mL of sample was withdrawn at 5, 10, 15, 20, and 30 min of time. 10 ml of buffer solution was used to replace to maintain the constant volume throughout the experiment. The samples were suitably diluted, and the percentage of drug released from each formulation was measured at 254 nm using UV-visible spectrophotometer.

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.

Stability studies

The selected optimized formulations were subjected to accelerated stability testing, tablets were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 40°C/75% RH for 3 months and evaluated for their physical appearance, drug content and drug excipient compatibility at specified intervals of time. The stability of optimized formulation 12 was investigated as per ICH guidelines. The formulation was stored at a temperature 40 ± 2°C and 75 ± 5% RH for 3 months.

RESULTS AND DISCUSSION

The formulation of orodispersible tablet was made using different superdisintegrants. Batches F1-F13 were prepared by direct compression method to select the disintegrant from the results. It can be confirmed that tablet prepared with Ac-di-sol in combination with entragit (F12), as processed excipient was found to be the best superdisintegrants for the preparation of orlistat ODT formulations. Due to it has exhibited faster disintegration time and best dissolution profile when compared to other formulations.

The physical characteristics of tablet blend were evaluated for different derived properties such as a Db (between 0. 48 and 0.55 g/cm^3), DT (between 0.55 and 0.65 g/cm^3), and Carr's compressibility index (between 12 and 26) given in (Table 2). The results of angle of repose and compressibility indicated that the flowability of powder blend is significantly good. Orodispersible tablets were evaluated for tablet properties such as weight variation, hardness, friability, wetting time, disintegration time, and dissolution.

All the formulations passed weight variation test as the percent weight variation was within the pharmacopeial limits hardness were shown in the range

of 1.9 ± 0.35 - 2.8 ± 0.61 kg/cm² in all the formulations which indicated good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations, the friability value was <1% and meets the official limit. The physical parameters of tablet formulation were depicted in Table 3. The disintegration results of all the formulation were found to be within prescribed limits and satisfied the criteria of the orally dispersible tablet.

The *in vitro* drug release studies for all formulations were performed. The results revealed that the increase in the proportion of superdisintegrants was associated with an increase in the overall cumulative drug release rate. Release profile of F12 which contains 2% of Ac-di-sol in combination with entragit, were found to be satisfactory and drug release data for F10-F13 was shown in Figure 1.

Table 4 shows data on accelerated stability study which was carried out over a 3 months period for optimized formulation F12 and observed that all parameters were found to be within the limit and the drug was stable for 3 months at accelerated condition without any noticeable change and confirmed that F12 batch was the optimized formulation. The results of the stability studies revealed that there was no significant change in drug release, weight variation, disintegration time, and assay.

Table 2: Physical characteristics of powder blend

Formulation number	Db g/cm³	DT g/cm³	Carr's index %	Hausner ratio	Angle of repose
F1	0.52±0.015	0.65±0.075	20.02±0.052	1.25±0.038	34.2±0.021
F2	0.55±0.011	0.64±0.028	26.21±0.036	1.16±0.037	35.5±0.036
F3	0.49±0.031	0.57±0.025	14.04±0.064	1.16±0.069	33.2±0.027
F4	0.48±0.018	0.55±0.035	12.72±0.037	1.14±0.035	32.4±0.031
F5	0.50±0.012	0.58±0.038	13.79±0.064	1.16±0.041	33.0±0.021
F6	0.53±0.026	0.61±0.026	13.11±0.052	1.15±0.024	32.1±0.035
F7	0.49±0.031	0.55±0.029	10.90±0.048	1.12±0.026	33.5±0.040
F8	0.53±0.016	0.61±0.031	13.11±0.054	1.15±0.052	32.1±0.027
F9	0.53±0.029	0.66±0.035	19.69±0.045	1.24±0.089	31.8±0.035
F10	0.51±0.024	0.62±0.041	18.62±0.054	1.16±0.054	32.2±0.036
F11	0.52±0.027	0.64±0.056	19.12±0.039	1.12±0.039	32.5±0.042
F12	0.50±0.031	0.59±0.052	19.83±0.041	1.21±0.045	33.1±0.033
F13	0.49±0.012	0.55±0.038	19.69±0.064	1.25±0.041	33.0±0.028

All values are expressed as mean±standard deviation, *n*=3, Db: Bulk density

Table 3: Some physical parameters of tablets (mean±SD)

Formulation number	Hardness (Kg/cm²)	Friability (%)	Thickness (mm)	Disintegration time (sec)	Weightvariation (average weight) (mg)	Wetting time (sec)
F1	2.5±0.23	0.41±0.12	2.1±0.20	42±0.37	198.1±1.21	94±0.33
F2	2.3±0.41	0.46±0.19	2±0.25	300±0.42	199.2±1.04	82±0.31
F3	2.6±0.32	0.48±0.25	2.1±0.21	45±0.36	198.6±1.32	102±0.32
F4	2.1±0.27	0.42±0.26	2±0.32	35±0.66	201.4±1.25	83±0.52
F5	2.8±0.61	0.49±0.15	2.2±0.41	49±0.54	197.8±1.29	68±0.61
F6	2.5±0.70	0.45±0.18	1.9±0.27	300±0.60	199.1±1.36	90±0.72
F7	2.5±0.29	0.44±0.24	2.1±0.52	320±0.47	201.3±1.41	70±0.36
F8	1.9±0.35	0.48±0.26	1.9±0.73	358±0.54	199.1±1.32	57±0.50
F9	2.5±0.41	0.41±0.11	2.1±0.52	48±0.37	202.9±1.39	48±0.32
F10	2.2±0.45	0.42±0.15	2.1±0.45	18±0.36	198.7±1.28	68±0.62
F11	2.2±0.42	0.40±0.21	2.0±0.51	58±0.26	201±0.1.34	51±0.72
F12	2.4±0.51	0.48±0.26	2.2±0.46	16±0.34	200±1.9	60±0.68
F13	2.3±0.41	0.68±0.26	2.1±0.21	23±0.54	202.9±1.39	62±0.62

All values are expressed as mean±standard deviation, *n*=3, SD: Standard deviation

Table 4: Stability data of formulation 12 at 40±2°C/75±5% RH

Time in days	Physical changes	Percentage of drug content*±SD	Moisture content	Percentage of drug release *±SD (99.5% of release label claim in 30 min) (%)
1st day (initial)	Round, yellow color uncoated tablets with plain on both side	99.51±0.48	0.82	97.09
30th day	No changes	99.95±0.11	0.78	97.12
60th day	No changes	100.01±0.13	0.80	97.20
90th day	No changes	99.81±0.28	0.78	97.16

All values are expressed as mean±SD, *n*=3, SD: Standard deviation

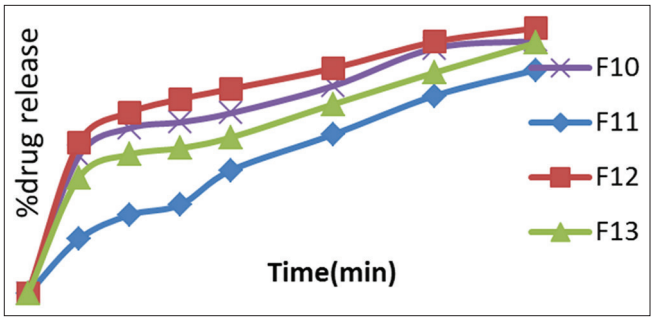

Figure 1: Graph of dissolution studies for formulation

CONCLUSION

Tablets prepared with 2% of Ac-di-sol in combination with entragit, as processed excipient was found to be the best superdisintegrants for the preparation of orlistat ODT formulations. Due to it has exhibited faster disintegration time and best dissolution profile when compared to other formulations in combination with crospovidone, microcrystalline cellulose, and sodium starch glycolate as superdisintegrants. At the end, it can be conclude that incorporation of pharmaceutical adjuvants in formulations has shown improved physicochemical properties of formulations and better patient compliance.

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