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DESIGN AND DEVELOPMENT OF NOVEL ORILISTAT CHEWABLE TABLETS FOR THE TREATMENT OF OBESITY

Sathya Surya Prasad Ch.[1*], J. Vijaya Ratna[2], M. Mohan Varma[3]

[1]Division of Pharmaceutical Technology, AU College of Pharmaceutical Sciences, Andhra University, Vishakhapatnam-530003, Andhra Pradesh, India.

[2]Division of Pharmaceutical Technology, Shri Vishnu College of Pharmacy, Bhimavaram, West Godavari, Andhra Pradesh, India.

[3]Sathya surya Prasad. Ch. Research scholar, Au College of Pharmaceutical sciences. Andhra University, Vishakhapatnam.

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***Corresponding Author**
Dr. Sathya Surya Prasad Ch.
Division of Pharmaceutical Technology, AU College of Pharmaceutical Sciences, Andhra University, Vishakhapatnam-530003, Andhra Pradesh, India.

ABSTRACT

Today in the world at the pharmacy plays a vital and critical role in deciding the major studies of obesity and mortality fail to show that overall obesity leads to greater risk. Orlistat is a novel, non-systemically acting anti-obesity agent used to treat obesity by preventing the absorption of fats from the human diet, thereby reducing caloric intake. The formulation tablet is a very complex process. Because of manufacturing defects due to low melting point sticky nature of the powder and stability of the API is poor. Now it's challenging task to obtain in tablet dosage form a new pharmaceutical form with acceptable organoleptic properties and stable dosage form for batter therapeutic action. The chewable tablets were prepared by melt granulation technique by using different fatty acids. And FT-IR, Differential scanning calorimetry, X-Ray diffraction and scanning electron microscopy were performed to identify the physicochemical interaction between drug and carriers.

KEYWORDS: Orlistat, chewable tablets, melt granulation method, fatty acids**.**

INTRODUCTION

Orlistat is a novel, non-systemically acting anti-obesity agent, it has a biological half-life of 1-2hr. Frequent administration of this agent is necessary due to its short biological half-life.

This selectively inhibits the absorption of approximately 30% of fatty components of the diet. Orlistat is prone to both hydrolysis and thermolysis, when stored in conditions above its melting point (42–44 °C), Orlistat is highly lipophilic and practically insoluble in water and is sticky nature of the powder it very difficult to formulate tablet. Hence, to deigned Orilistat chewable tablets to overcome all the above limitations. The Orlistat chewable tablet is expected to prove following benefits, to improve physical and chemical stability.

To improve therapeutic action, to treat obesity, for adolescents, to release the drug immediately at local sites for immediate therapeutic action, to minimize toxic effects, to reduce dose, to enhance solubility of the drug. To maintain long term stability of the dosage form to reduce costs by using simple techniques, to treat anti-obesity and type-2 diabetes, and hypertension and arthritis. To improve patient compliance. The present study polymers such as fatty acids are selected for to formulate stable chewable tablet by using melt granulation technique. The major objective of the present investigations to formulate and evaluate chewable Orlistat tablets selected as fatty acids by using melt granulation technique. These fatty acids are protecting the drug stability the reason is fatty acids are lower melting point than Orlistat before the drug the polymer is melted and to protect the drug degradation.

MATERIALS AND METHODS

Orlistat was a gift sample form Biocon pharmaceutical industry, Bangalore, India. Stearic acid, Palmitic acid, Lauric acid, Myristic acids and Mannitol are supplied from signet suppliers Mumbai in India. Methanol, Acetonitrile (HPLC), IPA, Ethanol, Ortho-phosphoric acids (88%), are supplied from Merck, Mumbai in India. Lactose, Talc, Magnesium stearate, SLS, SSG is supplied from S.D. Fine Chem limited, Mumbai in India. Sodium chloride, MCC is supplied from Chemiloids, Vijayawada in India. Cross carmallose, Calcium chloride, PEG, Povidone k30 are supplied from Bayir Chemicals, Bangalore in India. And melt granulation method.

Pre – Formulation studies

Differential scanning calorimetry (DSC)

The pure drug and solid dispersions were examined by DSC 60 (Shimadzu, Japan) where 5-6 mg samples were placed in an aluminium pan at a heating rate of 10 ^{0}C/min with the purging of dry nitrogen at a constant rate of 20 ml/min. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. DSC was used to determine crystallinity of orlistat.

Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) The scanning electron microscopy (SEM) analysis was carried out using scanning electron microscope (JSM 6100, Jeol, Japan). The scanning electron microscope was operated at an acceleration voltage of 20 KV, working distance (12–14 mm). The selected magnification was ×500. SEM was used to investigate particle shape of orilistat.

X-ray Powder Diffraction

X-ray Powder Diffraction (XRD) X-ray powder diffraction was used as a rapid analytical technique for detecting the amount of crystallinity in a powder sample. XRD patterns were recorded using Philips diffractometer Cu-ka radiation (l = 1.6418 Å).

FT-IR

The FT-IR (Shimadzu, Model 8033, USA) spectroscopy study was carried out at ambient temperature. The FT-IR analysis of pure drug and the tablet [F-D-I, II, III, IV, V, VI.] Were carried out by mixing the powder with KBr powder and granules and API were made by applying 6000kg/cm^2. FT-IR spectrums were obtained by powder diffuse reflectance on FT-IR spectrophotometer.

Table 1: FT-IR Studies Comparison of Different Functional Groups with API.

S. No.	Functional groups	Band range
1	-OH stretching unbound	3600-3400
2	C-H stretching aromatic	850-700
3	C-H alkanes stretching	2900-2850
4	C=O acids stretching	1700-1750
5	C-Cl	540-760

Analytical method development

Preparation of standard solution

Weigh accurately about 65 mg of Orilistat working standard into a 50 ml volumetric flask. Add 30 ml of dilute, sonicate to dissolve and dilute to volume diluent. Further dilute 5ml to 50 ml with the mobile phase.

Preparation of sample solution

Place one tablet in each vessel and carry out dissolution. Withdraw 10ml of aliquots, after each time interval replenish it with fresh dissolution media previously maintained at 37^{0}c.

Procedure

Inject blank (diluent), sample solution (in duplicate) into the chromatograph and record the chromatograms. Measure the area counts for Orlistat peak.

CALCULATION

$$= \frac{AT}{AS} \times \frac{\text{Std wt (mg)}}{50} \times \frac{5}{50} \times \frac{1000}{1\ \text{Tab}} \times \frac{\%\text{Potency of Std}}{100} \times \frac{100}{LC}$$

Table 2: Standard calibration curve for orilistat.

Injection Volume	Standard Area
10	34713
20	68397
25	85374
50	171049
75	253741
100	331449
120	419338
150	506494

Formulations of orlistat tablets

Formulation of Orlistat tablets by using fatty acids

Drug and fatty acids are weighed in accurately in different ratios. After weighing the Drug and fatty acids are melted at 30^0c. After melting to add reaming excipients and mixing thoroughly and dried at room temperature. Solid mass was pulverized and passed through sieve no. 22 to get uniform sized particles, the Formulations of fatty acids containing Orlistat with Stearic acid; Palmitic acid, Lauric acid and Myristic acid as a carrier in the different ratios were prepared by melting granulation method to compress the granules by using the 10 mm tolling kit.

Evaluation parameters

Hardness

The hardness of the tablet was measured using a Pfizer hardness tester. It is expressed in Kg/cm^2. (Tab 1).

Friability (F)

The friability of the tablet was measured using Roche Friabilator. It is expressed in percentage (%). 10 tablets were weighed ($W_{initial}$) and transferred to the Friabilator. The

Friabilator was operated at 25 RPM for 4 min. The tablets were weighed again (W_{final}). The % friability was then calculated by

$F = W_{intianal}-W_{final} / W_{intinal} \times 100$

Weight variation

Weight variation was carried out for both Chewable tablets. 20 tablets were weighed and the average weight was calculated. Then the tablets were weighed individually. The percentage weight deviation of each tablet from average weight was calculated using the following formula.

% Deviation = average weight − individual weight/average weight × 100

Thickness and diameter

The thickness and diameter of the tablets were measured by Screw Guage and expressed in millimeter.

Disintegration time of chewable tablet

The disintegration time of Chewable tablet was carried out using disintegration apparatus by using water as disintegration media maintained at 37^0C. When all the six tablets are completely disintegrated, the time was noted.

Drug content evaluation

60 mg equivalent weights of the granules were weighed and added3% SLS, 0.5% NaCl at pH 6.0 phosphate buffer and made up to 100 ml buffer. 1 ml of this solution is made up to 100 ml with buffer. Orlistat content in the granules was estimated by an HPLC method based on the measurement of absorbance at 205 nm.

RESULTS AND DISCUSSION

Table: 3 Pre-formulation parameters.

S. No.	Parameters	Observations
1	Orlistat	API
2	Angle of repose	21.81^0
3	Bulk density	0.432gm/cc
4	True density	0.532gm/cc
5	Tapped density	0.639gm/cc
6	Compressibility index%	25.15%
7	Cores index %	13.1%

8	Hausner`s ratio	1.15
9	Drug content	96.5%
10	Melting point	43^0 c
11	Particle size	16.19 nm

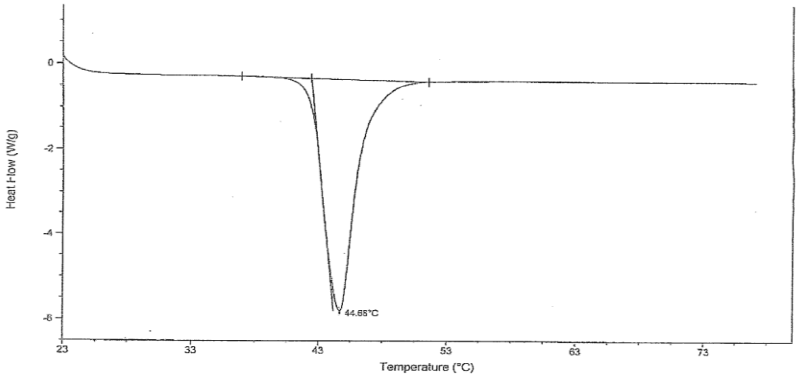


Fig 1: DSC image of orilistat pure drug. Orilistat showed a characteristic exothermic peak at 47^0c, which corresponds to its melting point.

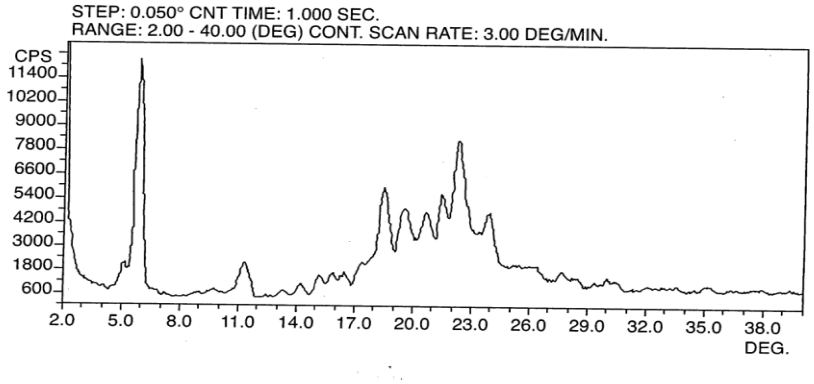


Fig 2: XRD image of orilistat pure drug. Orilistat showed a poor stability.

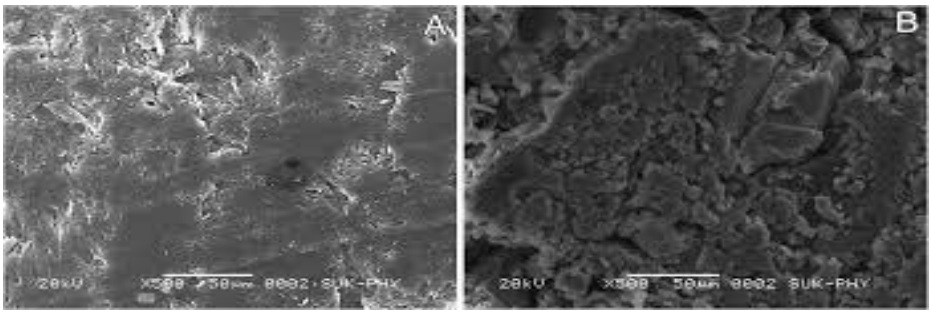


Fig 3: SEM image of orilistat pure drug. Orilistat showed morphological structure of the particle and the diameter of the particle.

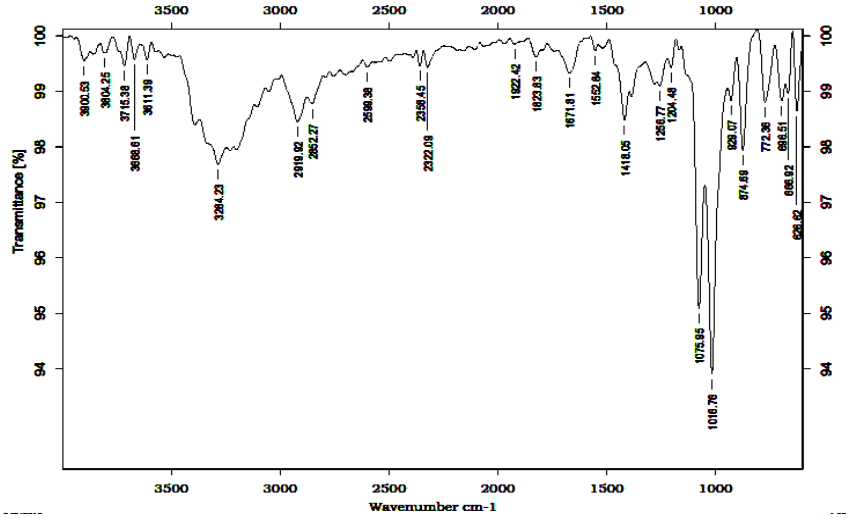


Fig 4: FT-IR reports of orilistat pure drug.

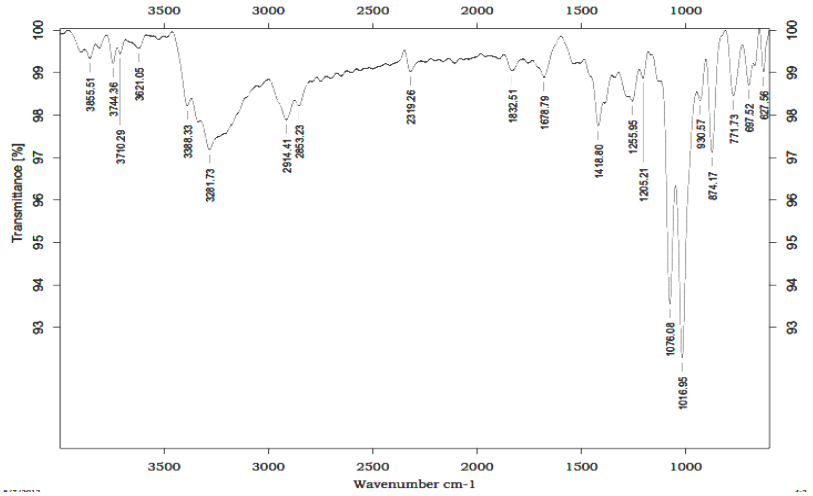


Fig 5: FT-IR reports of orilistat pure drug and stearic acid, there are no interactions between the orilistat and stearic acid.

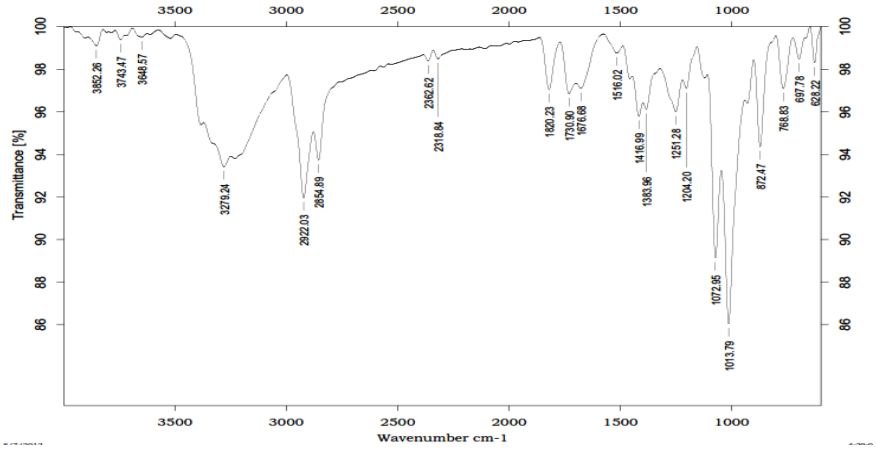


Fig 6: FT-IR reports of orilistat pure drug and palmitic acid, there are no interactions between the orilistat and palmitic acid.

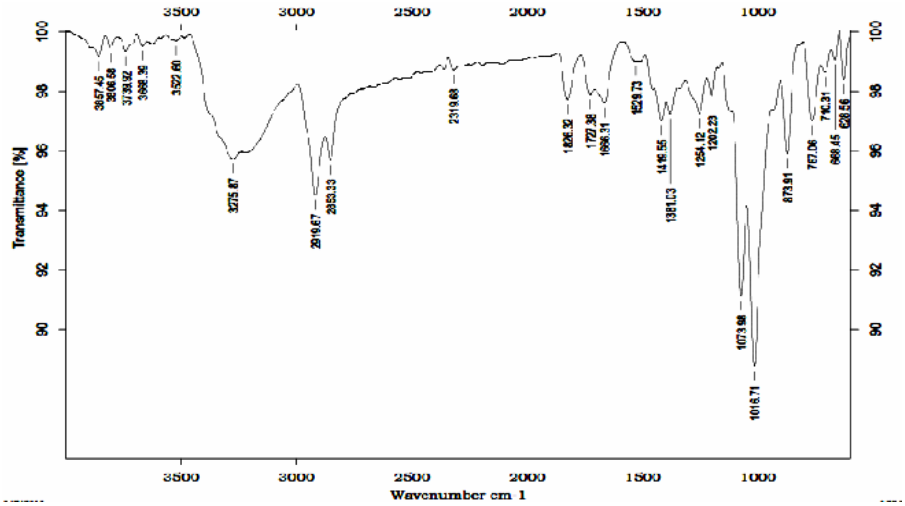


Fig 7: FT-IR reports of orilistat pure drug and lauric acid, there are no interactions between the orilistat and lauric acid.

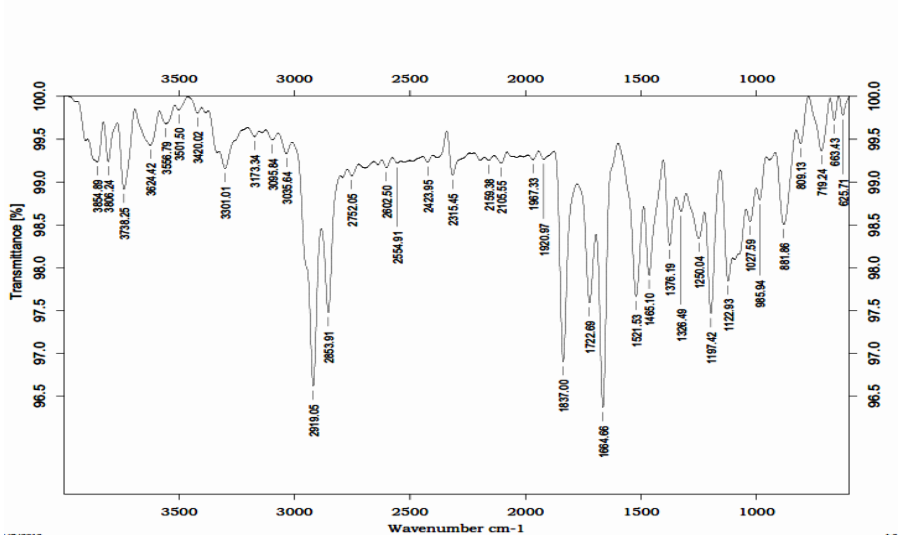


Fig 8: FT-IR reports of orilistat pure drug and Myristic acid, there are no interactions between the orilistat and Myristic acid.

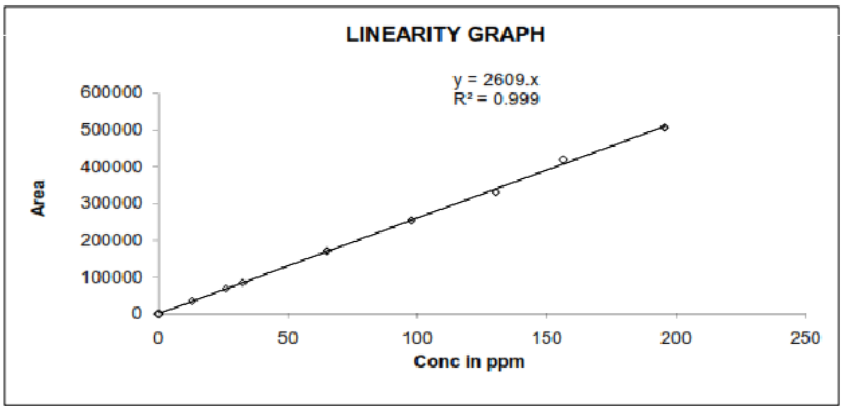


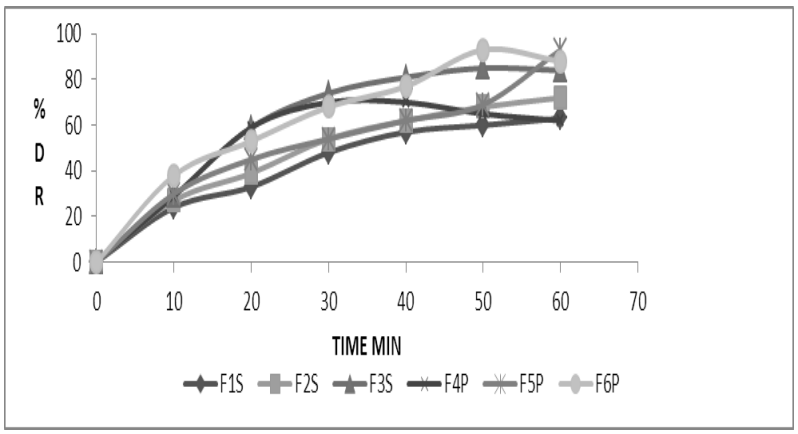
Fig 9: standard calibration curve for orilistat.

In vitro studies

Dissolution testing was performed using the HPLC. Rotating paddle apparatus in dissolution medium that was developed especially for Orilistat substance due to its hydrophobicity. The dissolution medium comprised an aqueous solution containing 3% of sodium lauryl sulphate, 0.5% of sodium chloride, adjusted to pH 6.0 with phosphoric acid, sink conditions were achieved because the solubility of orlistat in this medium is approximately 0.3 g in 100 ml. The rate of dissolution was determined, prepared Orlistat chewable tablet in a vessel with a paddle stirrer at75 RPM and containing 900 ml of medium. Aliquots of 10 ml were removed after 10, 20, 30, 40, 50 and 60 min. These aliquots were filtered in 0.45 micron size membrane filter and 10ml of the resultant clear solution was collected for assay by using HPLC.

Table: 4 Dissolution profile for Orilistat tablets prepared with various Fatty Acids.

Dissolution with 3%SLS in 0.5% NaCl, USP II, 900ml, 75 RPM, λmax 205 nm.								
		% Drug Release						
S.No.	**Formulations**	**Label Claim**	**10 min**	**20 min**	**30 min**	**40 min**	**50 min**	**60 min**
1	F_1 (S)	60	24	33	48	57	60	63
2	F_2 (S)	60	27	39	54	62	68	72
3	F_3 (S)	60	29	59	74	81	85	84
4	F_4 (P)	60	29	59	70	70	65	62
5	F_5 (P)	60	30	45	54	62	69	74
6	F_6 (P)	60	38	53	68	77	93	88
7	F_7 (L)	60	30	56	60	50	55	30
8	F_8 (L)	60	45	50	70	75	70	65
9	F_9 (L)	60	57	76	77	77	77	76
10	F_{10} (M)	60	75	80	84	89	90	73
11	F_{11} (M)	60	80	85	89	90	92	89
12	F_{12} (M)	60	88	96	96	95	94	93



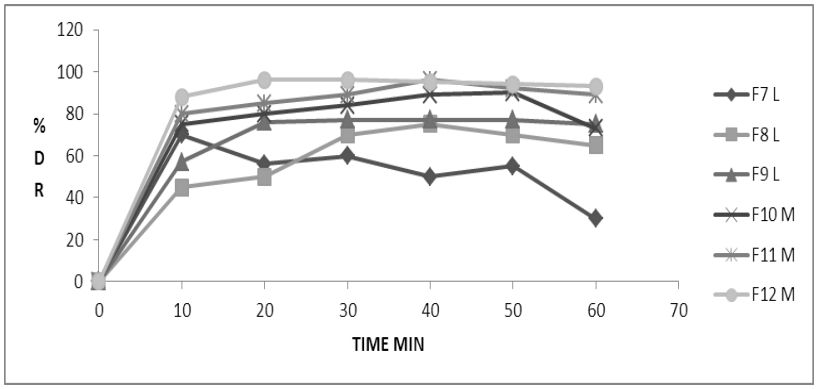


Fig 10: Dissolution Profile of Orilistat Tablets Prepared with various Fatty acids.

Table 5: Evaluation of orilistat tablets prepared with various Fatty Acids.

S.No.	Formulations	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)	Thickness (mm)	Disintegration Time (min)	Drug Content
1	F_1 (S)	4.0	0.50	900 ±5.0	5.60	2.5	90
2	F_2 (S)	4.0	0.45	900 ±5.0	5.63	2.6	91
3	F_3 (S)	4.0	0.60	900 ±5.0	5.68	3.0	93
4	F_4 (P)	4.0	0.55	900 ±5.0	5.69	2.9	94
5	F_5 (P)	4.0	0.60	900 ±5.0	5.60	2.6	90
6	F_6 (P)	4.0	0.59	900 ±5.0	5.64	2.5	93
7	F_7 (L)	4.0	0.50	900 ±5.0	5.60	2.5	90
8	F_8 (L)	4.0	0.45	900 ±5.0	5.63	2.6	91
9	F_9 (L)	4.0	0.60	900 ±5.0	5.68	3.0	93
10	F_{10} (M)	4.0	0.55	900 ±5.0	5.69	2.9	94
11	F_{11} (M)	4.0	0.60	900 ±5.0	5.60	2.6	90
12	F_{12} (M)	4.0	0.59	900 ±5.0	5.64	2.5	93

CONCLUSION

The present work chewable tablet containing Orlistat was successfully formulated using suitable excipients; to the delivery of drug in oral route from the study following conclusions should be the present study was carried out to develop chewable tablets containing Orlistat for immediate action. The selection of this approach by using fatty acids (Stearic acid, Myristic acid, Palmitic acid and Lauric acid) in different ratios. Among all these formulations $F_{12}M$ formula was fulfilled my objective of this work. The ability of the fatty acids to protect the drug and to maintain the stability is as follows.

Myristic acid >Palmitic acid > Stearic acid >Lauric acid

The preparation of the tablet the best method was optimized Melt granulation method.

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