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Formulation and Optimization of Pellets Containing Orlistat by Extrusion Spheronization

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ABSTRACT

The present study deals with the formulation and evaluation of Orlistat Pellets. Orlistat is a tetrahydrolipstatin designed to treat obesity by preventing the absorption of fats from the human diet, thereby reducing caloric intake. Orlistat was formulated in the form of pellets because pellets disperse freely in the GIT; they invariably maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects with out lowering drug bioavailability. Orlistat pellets were formulated using the technique of Extrusion. Extrusion eliminates dust during formulation and yields high quality pellets. Orlistat works by inhibiting pancreatic lipase, an enzyme that breaks down triglycerides in the intestine. Without this enzyme, triglycerides from the diet are prevented from being hydrolyzed into absorbable free fatty acids and are excreted undigested. In the formulation of orlistat pellets k-Carrageenan, PVPK-30, Deprogel, Sodium lauryl sulfate and Micro Crystalline Cellulose were used in different concentrations. The optimized pellets were studied for *invitro* drug release and assay using UV Spectroscopic technique. Moisture content was evaluated using Karl Fischer titration. Sieve Analysis was performed on optimized pellets. Bulk Density, Tapped Density and Carr's Index were determined. Characterization studies like FTIR, DSC and SEM were performed to know the drug-excipient interactions and surface morphology of the pellets. Accelerated stability studies were conducted on the optimized elongated pellets for 45 days. Dissolution Profile was compared with Marketed Product and results were determined accordingly.

Keywords: Extrusion Spheronization, orlistat, deprogel.

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INTRODUCTION

Obesity is defined as a body mass index (BMI) of 30 or more, where a person's BMI is defined as their weight in kg divided by the square of their height in meters. Overweight is defined as a BMI between 25 and 29.9. Overweight and obesity are diseases in which an excess of body fat has accumulated such that health may be adversely affected. They can cause and exacerbate many health problems, both independently and in association with other diseases. Orlistat inhibits pancreatic and gastric lipase thereby decreasing ingested triglyceride hydrolysis. It produces a dose-dependent reduction in dietary fat absorption thereby leading to weight loss in obese subjects. Orlistat, a pancreatic lipase inhibitor, reduces the absorption of dietary fat. It is used in conjunction with a mildly hypocaloric diet in individuals with a body mass index (BMI) of 30 kg/m2 or more *or* in individuals with a BMI of 28 kg/m2 in the presence of other risk factors such as type 2 diabetes, hypertension, or hypercholesterolemia. Some of the weight loss in those taking orlistat probably results from individuals reducing their Fat intake to avoid severe gastrointestinal effects including steatorrhoea. Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration. Extrusion-spheronization is a multiple-step compaction process, which includes the dry mixing of the ingredients with excipients, wet granulation, and extrusion, spheronization, drying, and screening to achieve the required size distribution. The Spheronizer is an instrument which is use to round up the material. Consisting of vertical hollow cylindrical (bowl) with a horizontal rotating disk (friction plate) located inside is, the most important component which can have a variety of surface texture designed for specific purpose. There are two patterns of the friction plate the cross-hatch and grid pattern. Spheronization typically begins with damp extruded particles, Granules from one of the extruders mentioned earlier. The extruded, cylindrically shaped particles are broken in to uniform length almost instantaneously and are gradually transformed in to spherical shape; this shaping process is akin to "plastic deformation" The present study deals with the formulation and evaluation of Orlistat Pellets using k-Carrageenan, PVPK-30, Deprogel, Sodium lauryl sulfate and Micro Crystalline Cellulose were used in different concentrations [1-8].

MATERIAL AND METHOD

Materials:

Orlistat was obtained as a gift sample from Meenaxi Pharma Pvt. Ltd. MCC from Asahi Kasei Corporation, k- Carrageenans from Rio Tinto Minerals, Sodium laurel Sulphate from Vinamax organics Pvt. Ltd, PVP-K-30 and Deprogel from S D Fine chemicals.

Method: By Extrusion Spheronization (Table 1)

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Table 1: Orlistat Formulation (Wt In: % W/W)

INGREDIENTS (gm)	AO1	AO2	AO3	AO4	AO5	AO6	AO7	AO8
MCC	40	30	20	30	20	10	5	----
k-CARRAGENAN	----	----	----	10	20	30	35	40
DEPROGEL	3	6	9	3	3	3	3	3
SLS	3	6	9	3	3	3	3	3
PVP-K30	4	8	12	4	4	4	4	4
TOTAL Wt(gm)	100	100	100	100	100	100	100	100

Drug-Excipients Compatibility Study by FTIR

The physicochemical compatibilities of the drug and the used excipients were tested by FTIR. Physical mixture of drug and excipients were taken into consideration for FTIR study.FTIR spectral analysis of pure drug and drug-polymer mixture was carried out by KBr disc method.

EVALUATION OF PELLETS

DISSOLUTION:

Dissolution Parameters:

Medium : 3% SLS (pH 6.0 Buffer), 900ml
Apparatus : Type II (Paddle)
RPM : 75
Temp : 37^{o} C

Buffer preparation (ph 6):

Weigh accurately 3% of sodium lauyrl sulfate and 0.5% sodium chloride in 1 liters of purified water, add 1 drop of n-octanol and adjust the pH to 6.0 with phosphoric acid.

Standard preparation:

Weigh accurately about 13mg of ORLISTAT working std into a 100 ml Vol flask. Add 2 ml of Acetonitrile and make up to the mark with dissolution medium (3%SLS – 6.0 pH).

Test preparation:

Transfer an amount of pellets equivalent to 120 mg of ORLISTAT into each vessel containing 900 ml of pH 6.0 buffer. Tap the pellets gently to make them settle to the bottom. After completion of specified time withdraw equal volume of sample and filter it.

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RESULTS AND DISCUSSIONS

The angle of repose of all batches were found below 30 ° which indicated the pellets having excellent flow property (Table 2).The Compressibility Index and Hausner ratio of all batches were calculated. On the basis of obtained values we can conclude that, the pellets of batches AO1- AO8 will have excellent flow property. Orlistat loaded pellets were prepared by using different polymers like MCC and k- Carrageenan. The data generated from the study revealed that concentration and physicochemical properties of different polymers influenced the release of orlistat from different batches of pellets. The initial batches AO1-AO3 were prepared using MCC purely, no k-carrageenan was used, the pellets show less drug dissolved due to less disintegration; though the concentration of superdisintegrant is increased. From batch AO4-AO8 the concentration of MCC was decreased and concentration of k-carrageenan was increased. This showed the increased drug dissolved, leading to good effect. The FTIR study shows that the drug and polymers are compatible with each other (fig 4). The batch AO8 was found to be good and effective. The pellets form batches AO8 were good in appearance but surface was slightly porous. The optimized formulation (AO8), when subjected to Stability studies at 25 ± 2 °C, 30 ± 2 °C, and 40 ± 2 °C, showed no significant changes in the physical and chemical properties, which confirms that the formulation (AO8) was stable at the end of 45 days (Table 7.) [9-14].

Table 2: Determination of micromeritics of ORLISTAT pellets.

Batch code	Angle of Repose(θ)(°)	Bulk Density(g/cm^2)	Tapped Density(g/cm^2)	Compressibility Index (%)	Hausner Ratio
AO1	28.81	0.75	0.82	8.53	1.09
AO2	29.68	0.76	0.84	9.52	1.10
AO3	27.92	0.68	0.75	9.33	1.11
AO4	28.81	0.75	0.80	6.25	1.06
AO5	26.56	0.77	0.82	6.09	1.06
AO6	27.74	0.68	0.71	4.2	1.04
AO7	26.10	0.57	0.63	9.52	1.11
AO8	27.02	0.56	0.61	8.1	1.08

Table No 3: Comparative *In vitro* Drug Dissolved Profile of Batch AO1 to AO8

Time (min)	Cumulative % Drug Dissolved							
	AO1	**AO2**	**AO3**	**AO4**	**AO5**	**AO6**	**AO7**	**AO8**
0	0	0	0	0	0	0	0	0
20	16.5	19.2	22.3	27.5	22.4	22.5	25.4	32.1
40	28.3	34.8	37.8	39.4	31.5	31.6	37.5	43.5
60	39.5	46.0	43.4	51.4	39.5	41.9	49.1	54.7
80	48.6	54.4	53.5	60.0	48.6	51.7	57.2	63.4
100	58.2	62.4	64.1	70.3	61.0	64.8	68.0	73.0
120	65	66.7	73.5	77.8	70	72.3	75.7	81.0
140	68.3	73.4	76.3	85.6	77.4	79.6	83.1	88.9
160	70.9	75.4	80.2	90.9	82.1	84.6	87.3	94.3

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Table No 4: Comparative In vitro Drug Dissolved Profile of Batch AO8 and Marketed Product

Sr. No.	Time (min)	AO8	Marketed Product (XENICAL)
1	0	0	0
2	20	32.1	29.15
3	40	43.5	41.66
4	60	54.7	53.21
5	80	63.4	60.41
6	100	73.0	75.55
7	120	81.0	78.20
8	140	88.9	87.02
9	160	94.3	93.01

Table No 5: % Drug Content (Assay) of Different Batches of Orlistat and Marketed Product.

Sr. No.	Formulation	% Drug Content
1	AO1	97.35± 1.02
2	AO2	96.99± 1.66
3	AO3	99.26 ± 1.42
4	AO4	98.55 ± 0.92
5	AO5	97.95 ± 1.58
6	AO6	98.22 ± 0.62
7	AO7	97.67 ± 0.57
8	AO8	99.85 ± 0.66
9	Marketed Product	99.56±0.55

Table 6: Interpretation of FTIR.

Functional group	Standard Range (cm-1)	Orlistat (cm-1)	Orlistat and MCC (cm-1)	Orlistat and Carrageenan (cm-1)	Orlistat and Deprogel (cm-1)
C=O stretching	1700–1725	1708	1710.7	1709.6	1710.5
C–H stretching in CH2	2850–2960	2920	2920	2923.1	2921.5
N–H stretching	3500–3300	3336.6	3338.6	3337.8	3337
C–H deforming	875–895	877.7	877.5	878.2	877
C=C aromatic stretching	1450–1600	1521.7	1458.1	1462	1466

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Table 7: Stability Studies of Formulation AO8 at Various Storage Temperatures and Ambient Humidity.

STORAGE CONDITION			
	25 ± 2 °C	30 ± 2 °C	40 ± 2 °C
Sampling interval (days)	Drug Content	Drug Content	Drug Content
01	98.55 ± 1.02	98.55 ± 1.02	98.55 ± 1.02
15	97.98 ± 0.22	97.75 ± 2.02	97.64 ± 2.22
30	97.93 ± 1.42	97.67 ± 1.02	96.75 ± 2.02
45	96.54 ± 2.22	97.55 ± 2.22	96.05 ± 2.42

Results are the mean ± SD (n = 3)

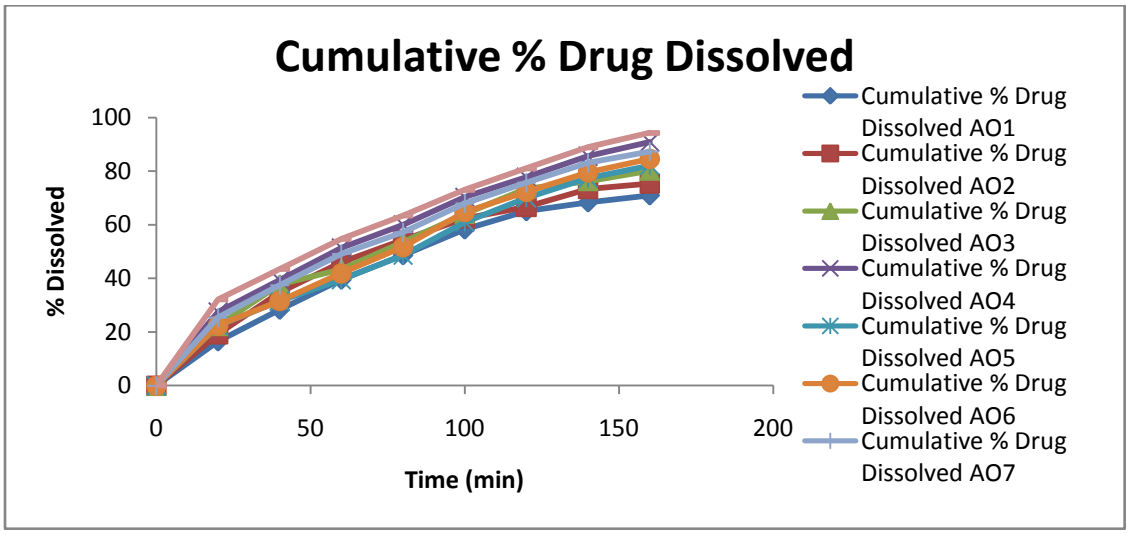

Fig 1: Comparative % drug dissolved of different batches of Orlistat pellets.

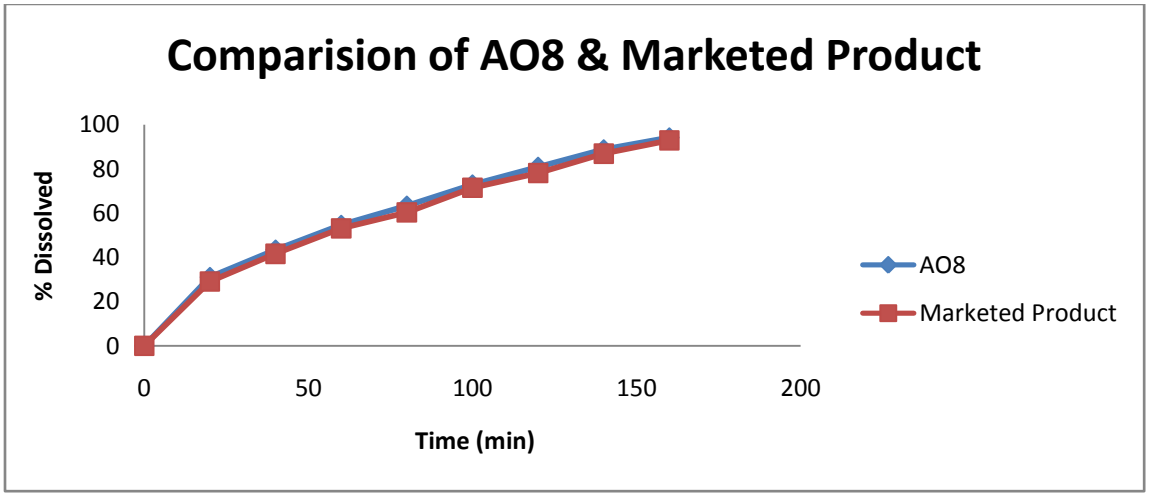

Fig 2: Comparative % drug dissolved of batch AO8 of Orlistat pellets and marketed product.

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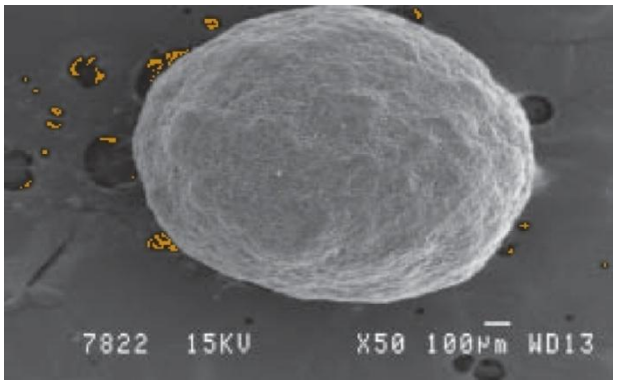
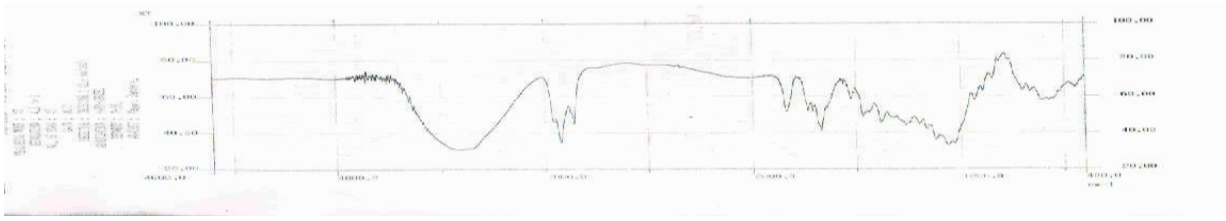
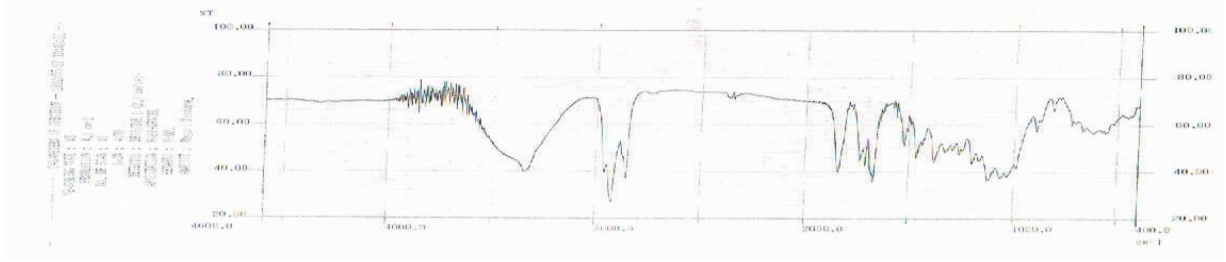


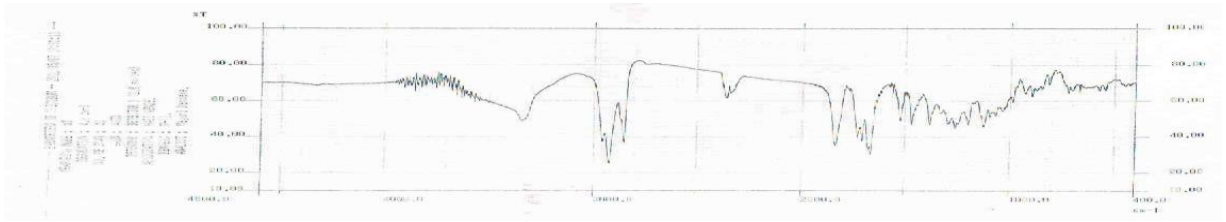
Fig 3: SEM of pellets at 50X magnification



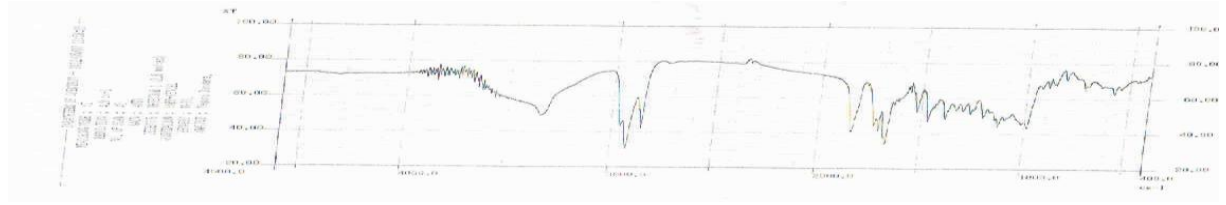
4.1a) FTIR of drug orlistat



4.1b) Mixture of orlistat and MCC



4.1c) Mixture of orlistat and carrageenan



4.1d) Mixture of orlistat and deprogel

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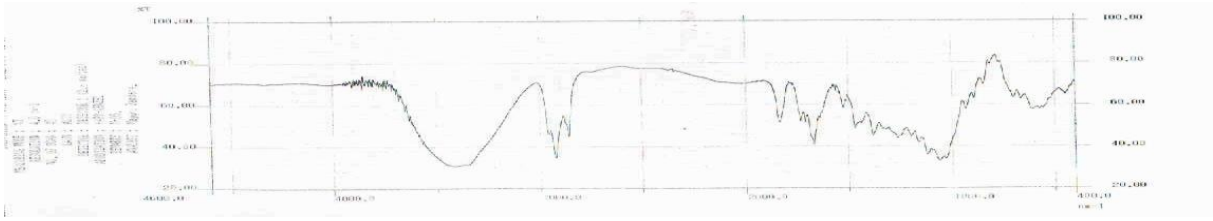

4.1e) Drug and mixture of excipients

Figure 4: FTIR spectra of (a) orlistat; (b) mixture of orlistat and MCC; (c) mixture of orlistat and carrageenan; (d) mixture of orlistat and deprogel and (e) drug and mixture of excipients

CONCLUSION

In the present study we can conclude that orlistat pellets were successfully prepared by Extrusion Spheronization Technique using k-Carrageenan, PVPK-30, Deprogel, Sodium lauryl sulfate and Micro Crystalline Cellulose and their evaluation were carried out. K-carrageenan is a suitable pelletization agent for extrusion-spheronization as pellets with sufficient quality were achieved for all formulations. The k-carrageenan formulations always required higher water content during the pelletization process. All k-carrageenan pellets showed a fast disintegration of pellets resulting in fast release. Therefore, k-carrageenan is a suitable pelletization aid which increases the robustness of the process and it can be used as a substitute for the commonly used MCC. Drug release from the developed formulations matched with Innovator and also found to be stable formula.

ACKNOWLEDGEMENTS

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