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Fabrication and characterization of Orlistat Liquisolid tablets

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Abstract
The aim of the work was to improve the dissolution properties of the practically insoluble anti-obesity drug, Orlistat by utilizing liquisolid technique. Different liquisolid tablets were prepared by dissolving Orlistat in PG with Avicel PH 102 as carrier, Aerosol 200 as coating material and Sodium starch glycolate as disintegrating agent. Additives such as PVP, HPMC and HPG were incorporated into the formulations to improve dissolution characteristics. The formulated liquisolid tablets were evaluated for post compression parameters such as weight variation, hardness, friability, drug content and *in-vitro* dissolution studies. FT-IR study suggested that there was no chemical interaction between the drug and excipients. DSC was performed to evaluate the physicochemical properties of the liquisolid tablets, which confirm the conversion of crystalline form of the drug to the amorphous form in liquisolid tablets. The result showed that liquisolid formulation of Orlistat exhibited higher percentage of drug release than directly compressed tablets which show significant benefit of liquisolid tablet in increasing wetting properties and surface area of drug available for dissolution.

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Keywords: Aerosil 200, Anti-obesity, Avicel PH 102, *in-vitro* dissolution, liquisolid tablets, Orlistat

Introduction

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. Body mass index (BMI), a measurement which compares weight and height, defines people as overweight (pre-obese) if their BMI is between 25 kg/m^2 and 30 kg/m^2, and obese when it is greater than 30 kg/m^2. BMI is calculated by dividing the subject's mass by the square of his or her height, typically expressed either in metric or US "customary"- unit. [1]

Effects and Complications of Obesity

- High cholesterol and atherosclerosis (where fat is deposited in arteries), which can lead to coronary heart disease and stroke asthma.
- Metabolic syndrome – a combination of diabetes, high blood pressure and obesity.
- Breathing disorders, including sleep apnea, a potentially serious sleep disorder in which breathing repeatedly stops and starts.
- D stiffness in joints.

Liquisolid Technique

The liquisolid technique as described by Spireas [16] is a novel concept, where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material.

The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicle, is included into the porous carrier material.
Inert, preferably water-miscible organic solvent systems with high boiling point such as liquid polyethylene glycols, propylene glycol, or glycerin are more suitable as liquid vehicles. As the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles.

Objectives of the present study

- To improve the solubility and thereby dissolution rate of poorly water soluble anti- obesity drug Orlistat using liquisolid technique.
- To prepare liquisolid tablets of Orlistat using various nonvolatile solvents.
- To study the solubility of Orlistat in different non-volatile solvents.
- To study the pre-compression characteristics of the liquisolid system.
- To evaluate the post-compression parameters of liquisolid tablets.
- To compare the *in-vitro* drug release profile of the prepared liquisolid tablets. To study the influence of the different excipients on the drug release profile of the liquisolid systems.
- To compare the drug release profile of prepared liquisolid tablets with directly compressed tablets.
- To conduct the stability studies of the optimized formulation as per the ICH guidelines.

Materials

Table 1: List of chemicals and excipients

SL No.	Materials	Manufacturer or Supplier
1.	Orlistat	Hetero Drugds Hyderabad
2.	Microcrystalline cellulose (Avicel pH 102)	S.D Fine Chemicals Pune
3.	Silicon dioxide	S.D Fine Chemicals Pune
4.	Lactose Monohydrate	S.D Fine Chemicals Pune
5.	Sodium starch glycolate	S.D Fine Chemicals Pune
6.	Magnesium stearate	S.D Fine Chemicals Pune
7.	Polyethylene glycol 200, 400, Tween 80, Propylene glycol	S.D Fine Chemicals Pune
8.	Polyvinyl pyrrolidone	S.D Fine Chemicals Pune
9.	Hydroxy Propyl Methyl Cellulose	S.D Fine Chemicals Pune
10.	Hydroxy Propyl guar	S.D Fine Chemicals Pune
11.	Methanol	SpectroChem PVT. LTD.

Table 2: List of instruments used

S. No.	Instruments	Manufacturer or Supplier
1.	Digital weighing balance	Shimadzu, Acculab
2.	UV visible spectrophotometer	UV-1800, Shimadzu UV spectrophotometer.
3.	Tablet compression machine	Rimek RSB-4 minipress.
4.	Hardness tester	Pfizer hardness tester.
5.	pH meter	Eutech instruments
6.	Roche friabilator	Electrolab tablet friability tester.
7.	Tablet disintegration tester	Labindia
8.	Dissolution test apparatus	Electrolab TDT-06T dissolution tester.
9.	FTIR	IRAffinity-1S FT-IR, Shimadzu.
10.	DSC	DSC-60 Plus, Shimadzu.
11.	Programmable environmental test chamber	Remi instruments

Drug Profile

Orlistat

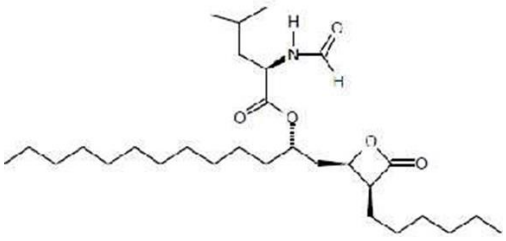

Fig 1: Structure of orlistat

Molecular formula: C29H53NO5
Molecular weight: 495.735
Solubility: Freely soluble in chloroform, very soluble in methanol and poorly soluble in water.

Description: Orlistat is the saturated derivative of lipstatin, a potent natural inhibitor of pancreatic lipases isolated from the bacterium Streptomyces toxytricini. However, due to its relative simplicity and stability, orlistat was chosen over

lipstatin for development as an anti-obesity drug.
Category: Anti-obesity

Formulation of Orlistat tablets by direct compression
Orlistat tablets were prepared by direct compression. All the ingredients were weighed individually, then mixed uniformly followed by the addition of magnesium stearate and talc. The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and hausner's ratio. After evaluation of the powder blend, the tablets were compressed.

Table 3: Formulation of orlistat tablets

Ingredients	Quantity/ Tablet (mg)
Orlistat	60
Microcrystalline cellulose	135
Lactose monohydrate	50
Aerosil	15
Sodium starch glycolate	10
Magnesium stearate	10

Table 4: Formulation table of liquisolid compacts of orlistat

Liquisolid System Code	Carrier: Coating (R)	Liquid Load Factor (Lf)	Non-Volatile Solvent (mg)	Active Ingredient (mg)	Weight Of Liquid Medication (mg)	Carrier (mg)	Coating (mg)	Disintegrant (mg)	Lubricant (mg)	Additives (mg)	Unit Dose Weight (mg)
LS-1	10.66	0.625	40	60	100	160	15	10	10	-	295
LS-2	12	0.694	40	60	100	144	12	10	10	-	276
LS-3	15	0.66	40	60	100	150	10	10	10	-	280
LS-4	16.5	0.6	40	60	100	165	10	10	10	-	295
LS-5	21.25	0.58	40	60	100	170	8	10	10	-	298
LS-6	26	0.64	40	60	100	156	6	10	10	-	282
LS-7	13	0.76	40	60	100	130	10	10	10	30 (PVP)	290
LS-8	13	0.76	40	60	100	130	10	10	10	30(HPMC)	290
LS-9	13	0.76	40	60	100	130	10	10	10	30 (HPG)	290

Assay
The Orlistat content in each formulation was analyzed using Shimadzu (UV – 1800) UV Visible spectrophotometer by random selection of 5 tablets from each batch. The measurement for each formulation was done thrice and the average of them was calculated and expresse in %.
Procedure: 5 tablets were selected by fortuitous from the lot, triturated to get fine powder. 50mg equivalent of Orlistat was dissolved in 50ml of methanol. 5ml of the above solution was withdrawn and the volume was made upto 50ml with methanol. Then the absorbance was measured at 202 nm. The concentration of drug present in the sample was determined by using the slope value.

***In-vitro* Dissolution Studies**
In-vitro release studies were carried out using tablet dissolution test apparatus. Two objectives in the development of *in-vitro* dissolution tests are to show (1) that the release of the drug from the tablet is complete and (2) that the rate of drug release is uniform batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective.
The following procedure was employed throughout the study to determine the *in-vitro* dissolution rate for all the formulations.

- Apparatus - USP Type II (Paddle type).
- Dissolution medium - 900 ml of 0.1N HCl
- Temperature - 37±0.50C
- RPM - 50
- Volume withdrawn - 5 ml
- Time interval - 10, 20, 30, 40, 50 and 60 minutes interval
- λ max - 202 nm
- Beer's range - 10-100 µg/ml

Stability Studies
The selected formulations were subjected to stability studies by placing it in a tightly closed amber colored glass container and storing in a stability chamber. The formulations were stored at different storage conditions like 5^0C Ambient, 25^0C/ 60 % RH and 40^0C/ 75 % RH for 30 days. The formulations were subjected to different tests namely hardness, drug content and *in-vitro* drug release studies after 30 days.

Results
UV Spectrum of Orlistat

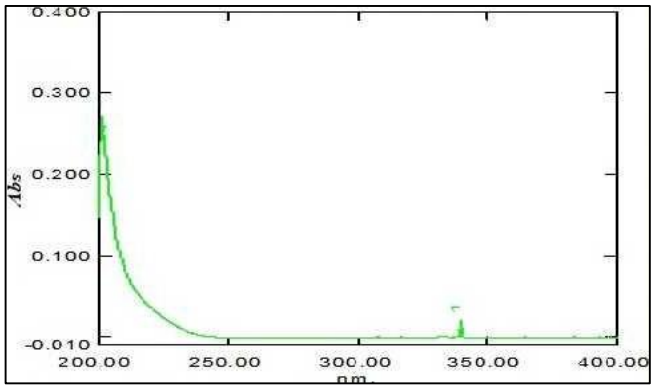

Fig 2: UV spectra of orlistat

The preliminary investigation of Orlistat was carried out using methanol and the maximum absorbance was measured at 202nm. The regression coeffient was found to be 0.9962. The slope value was 0.0055, which was used in the calculation of %CDR.

Table 5: Calibration curve data for orlistat in methanol

S. No.	Vol of SSII (ml)	Vol made upto (ml)	Conc. (µg/m)	Absorbance @ 202nm			AVG abs	±SD
				Trial 1	Trial 2	Trial 3		
1	1	10	10	0.133	0.141	0.135	0.136	0.00416
2	2	10	20	0.169	0.165	0.166	0.166	0.00208
3	3	10	30	0.219	0.222	0.22	0.220	0.00152
4	4	10	40	0.27	0.273	0.271	0.271	0.00152
5	5	10	50	0.312	0.325	0.322	0.319	0.00680
6	6	10	60	0.395	0.39	0.391	0.392	0.00264
7	7	10	70	0.448	0.452	0.45	0.45	0.002
8	8	10	80	0.498	0.501	0.499	0.499	0.00152
9	9	10	90	0.556	0.558	0.557	0.557	0.001
10	10	10	100	0.617	0.62	0.623	0.62	0.003

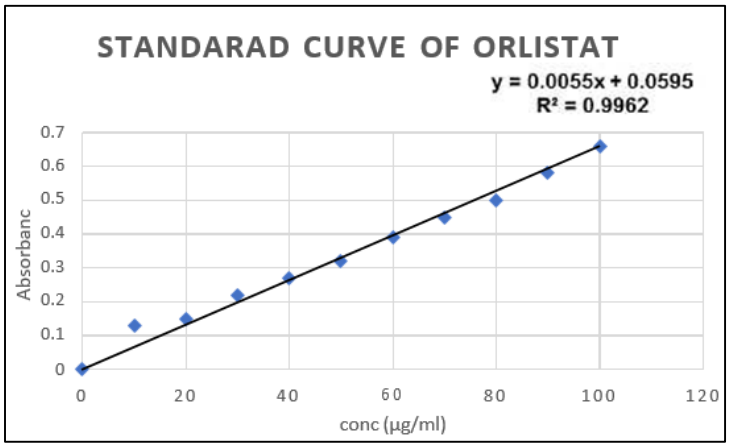

Fig 3: Calibration curve for orlistat

Compatibility Studies

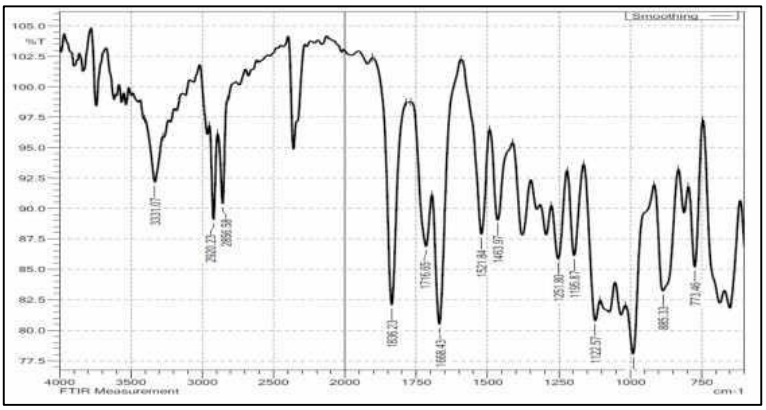

Fig 4: FT-IR spectra of orlistat

Fourier transform infrared spectroscopy

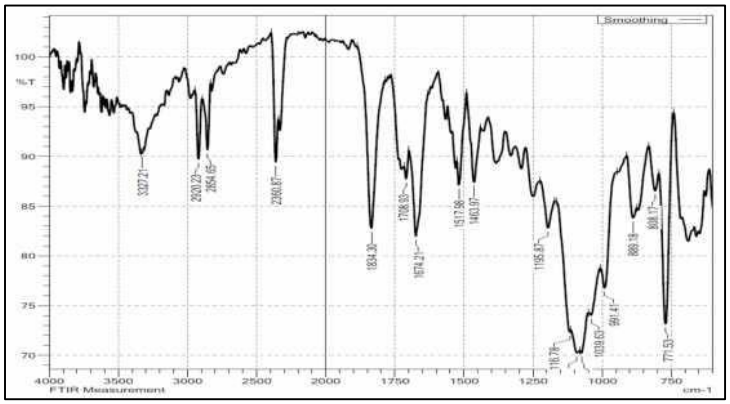

Fig 5: FT-IR spectra of the optimized formulation

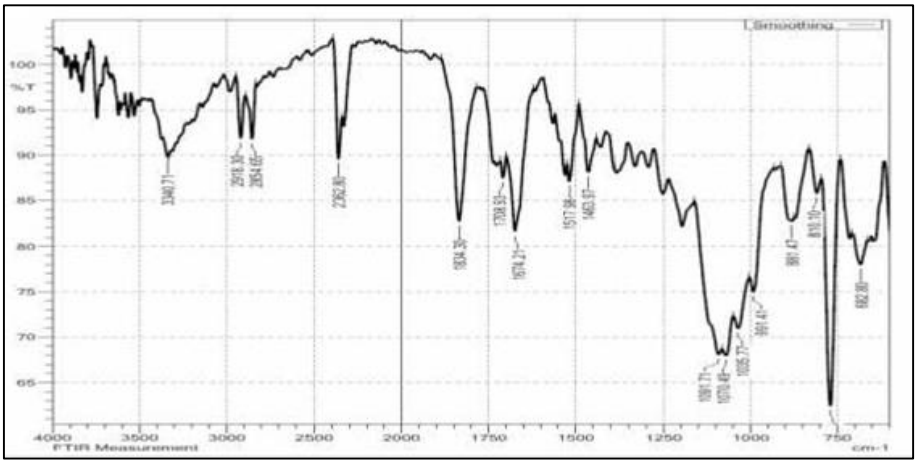

Fig 6: FT-IR spectra of directly compressed tablets

Table 6: Comparison of FT-IR spectra of pure drug with optimized formulation

Functional groups	Characteristic peaks in cm-1	
	Orlistat	Optimised formulation
C=0 Stretching	1716.65	1708.93
C-H Stretching in CH2	2920.23	2920.23
N-H Stretching	3331.07	3327.21
C-H Deforming	885.33	889.18
C=C Aromatic stretching	1521.84	1517.98
C-N Stretching	1195.87	1195.87

Differential scanning calorimetry

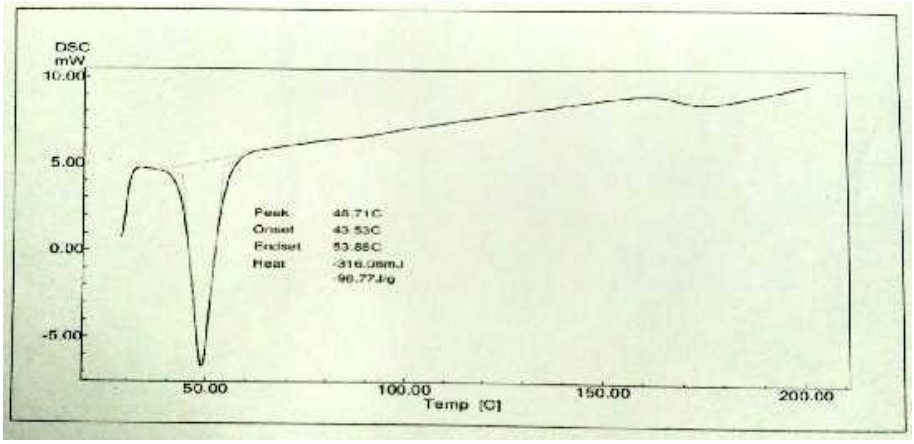

Fig 7: DSC spectra of orlistat

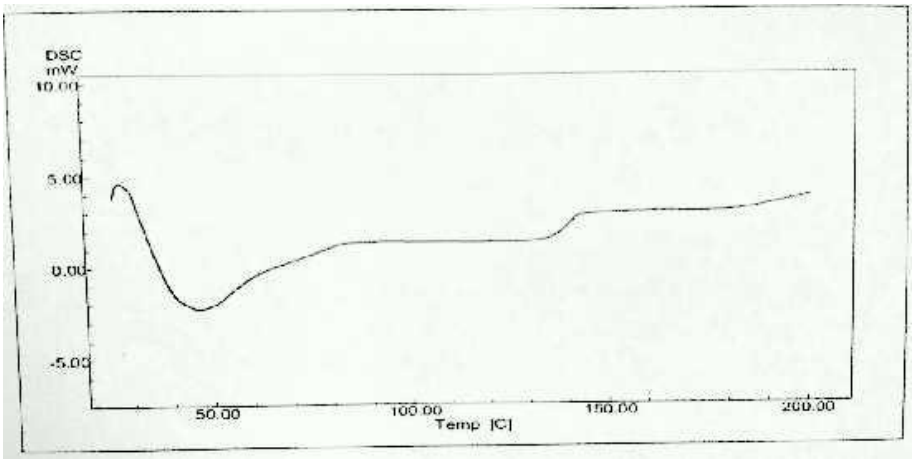

Fig 8: DSC spectra of the optimized formulation

Solubility Studies

Table 7: Solubility of orlistat in various non-volatile solvents

SL. No	Solvent	Solubility (mg/ml)
1	Propylene glycol	57.72
2	PEG 200	50.9
3	PEG 400	48.62
4	Tween 80	53.18

Pre-compression parameters

Table 8: Pre-compression parameters

Liquisolid formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose
LS-1	0.454	0.526	13.68	1.15	30.4^0
LS-2	0.444	0.526	15.58	1.18	32.4^0
LS-3	0.454	0.555	18.19	1.22	27.82^0
LS-4	0.465	0.555	16.21	1.19	33.69^0
LS-5	0.454	0.540	15.92	1.18	31.21^0
LS-6	0.465	0.526	11.59	1.13	29.05^0
LS-7	0.476	0.571	16.63	1.19	32.4^0
LS-8	0.465	0.526	11.59	1.13	30.57^0
LS-9	0.465	0.555	16.21	1.19	31.21^0
DCT	0.454	0.540	15.92	1.18	32.15^0

Post-compression parameters

Table 9: Post-compression parameters

Formul ation Code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	% Drug Content	DT (secs)	Weight Variation (%)
LS-1	4.20±0.06	4.1±0.1	0.40	94.7±0.2	276	-0.92 to +0.77
LS-2	4.04±0.02	3.9±0.1	0.61	95.09±0.1	250	-0.86 to +0.95
LS-3	4.20±0.05	3.7±0.1	0.60	93.1±0.3	245	-0.71 to +1.0
LS-4	4.46±0.03	4.3±0.11	0.38	96.5±0.2	288	-0.67 to +0.67
LS-5	4.47±0.036	4.3±0.15	0.32	95.8±0.1	275	-0.79 to +0.34
LS-6	4.04±0.025	3.7±0.15	0.62	94.9±0.15	242	-0.89 to +0.17
LS-7	4.11±0.02	4.1±0.36	0.50	97.0±0.3	276	-0.65 to +0.71
LS-8	4.05±0.005	3.9±0.2	0.48	98.1±0.15	255	-0.83 to +0.88
LS-9	4.27±0.015	4.1±0.25	0.49	96.7±0.25	270	-0.79 to +0.92
DCT	4.14±0.011	4.5±0.34	0.32	98.5±0.3	295	-0.75 to +1.02

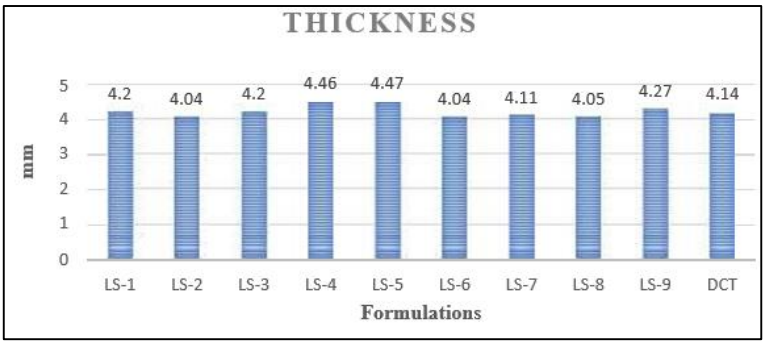

Fig 9: Graphical representation of thickness

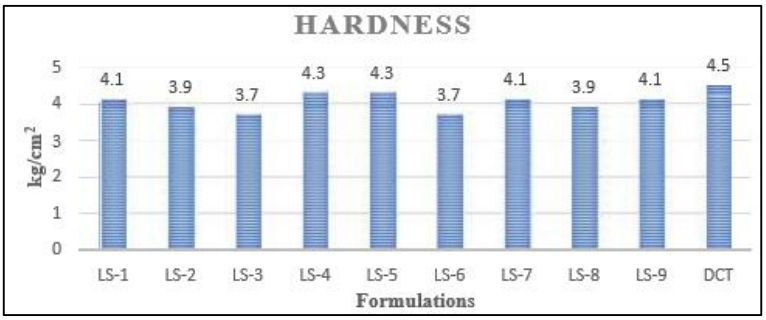

Fig 10: Graphical representation of hardness

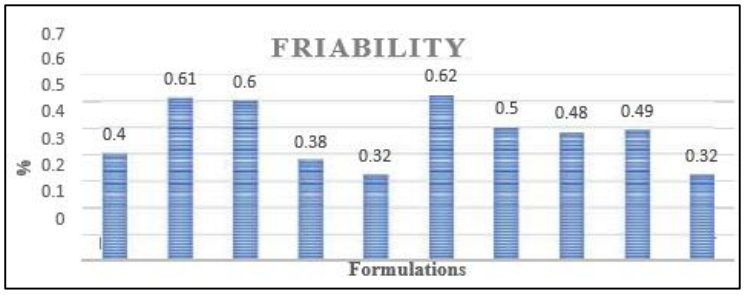

Fig 11: Graphical representation of friability

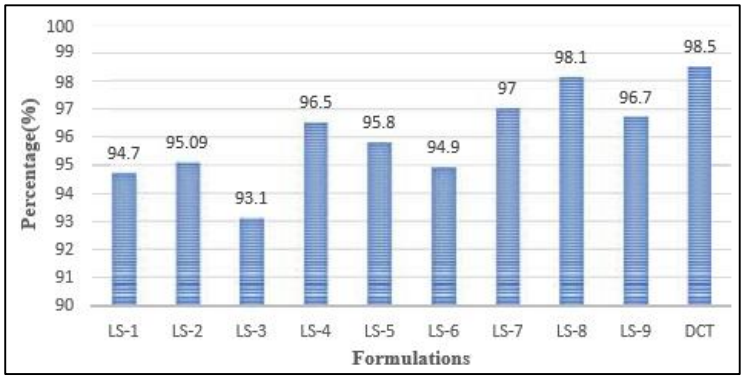

Fig 12: Graphical representation of % drug content

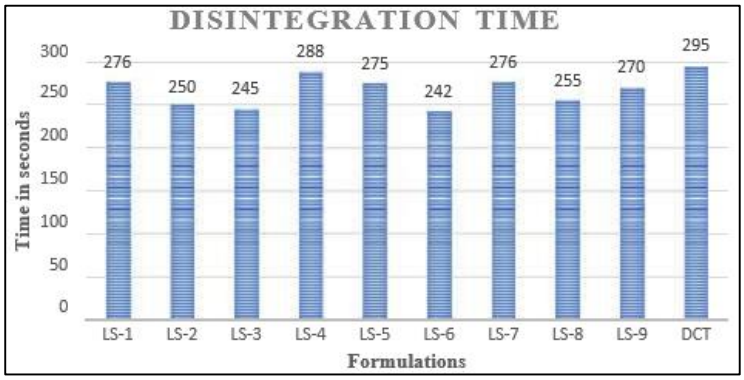

Fig 13: Graphical representation of disintegration time

In-vitro dissolution studies

- Apparatus- USP Type II (Paddle type).
- Dissolution medium - 900 ml of 0.1N HCl
- Temperature - 37±0.5^{0}c
- RPM- 50
- Volume withdrawn - 5 ml
- Time interval - 10, 20, 30, 40, 50 and 60 minutes interval
- λmax- 202 nm
- Beer's range - 10-100 µg/ml

Table 10: *In-vitro* drug release profile of ls-1

Time	Abs	Conc µg/ml	Amt 10ml	Amt 900ml	CLA	CDR	%CDR
0	0	0	0	0	0	0	0
10	0.052	9.45	0.094	17.01	0	17.01	29.95
20	0.094	17.09	0.170	30.76	0.094	30.85	54.30
30	0.124	22.54	0.225	40.58	0.265	40.84	71.88
40	0.136	24.72	0.247	44.50	0.490	45	79.19

Table 11: *In-vitro* drug release profile of ls-8

Time	Abs	Conc µg/ml	Amt 10ml	Amt 900ml	CLA	CDR	%CDR
0	0	0	0	0	0	0	0
10	0.042	7.63	0.076	13.74	0	13.74	23.35
20	0.095	17.27	0.172	31.09	0.076	31.16	52.95
30	0.129	23.45	0.234	42.21	0.249	42.46	72.14
40	0.161	29.27	0.292	52.69	0.483	53.17	90.34
50	0.168	30.54	0.305	54.98	0.776	55.75	94.73
60	0.172	31.27	0.312	56.29	1.081	57.37	97.47

Table 12: *In-vitro* drug release profile of dc tablets

Time	Abs	Conc µg/ml	Amt 10ml	Amt 900ml	CLA	CDR	%CDR
0	0	0	0	0	0	0	0
10	0.028	5.09	0.050	9.16	0	9.16	15.50
20	0.048	8.72	0.087	15.70	0.050	15.76	26.66
30	0.089	16.18	0.161	29.12	0.138	29.26	49.51
40	0.102	18.54	0.185	33.38	0.3	33.68	56.99
50	0.118	21.45	0.214	38.61	0.485	39.10	66.16
60	0.119	21.63	0.216	38.94	0.7	39.64	67.08

Table 13: *In-vitro* drug release profile of pure drug

Time	Abs	Conc µg/ml	Amt 10ml	Amt 900ml	CLA	CDR	%CDR
0	0	0	0	0	0	0	0
10	0.031	5.63	0.056	10.14	0	10.14	16.90
20	0.042	7.636	0.076	13.74	0.056	13.80	23.0
30	0.056	10.18	0.101	18.32	0.132	18.46	30.76
40	0.069	12.54	0.125	22.58	0.234	22.81	38.02
50	0.087	15.81	0.158	28.47	0.36	28.83	48.05
60	0.091	16.54	0.165	29.78	0.518	30.3	50.5

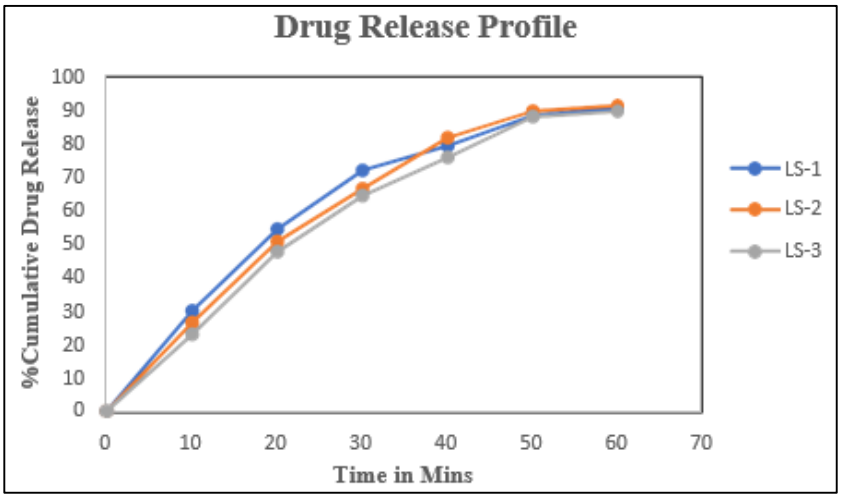

Fig 14: Graphical representation of *in-vitro* drug release profiles of Ls-1, Ls-2, Ls-3

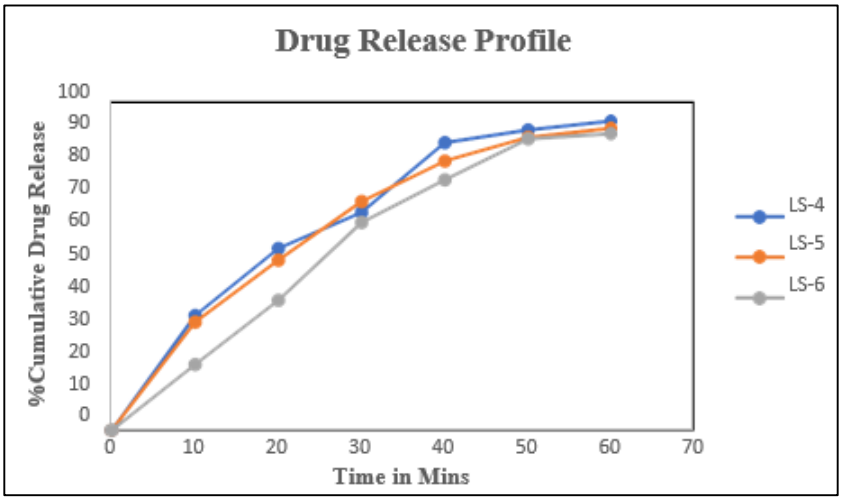

Fig 15: Graphical representation of *in-vitro* drug release profiles of LS-4, LS-5, LS-6

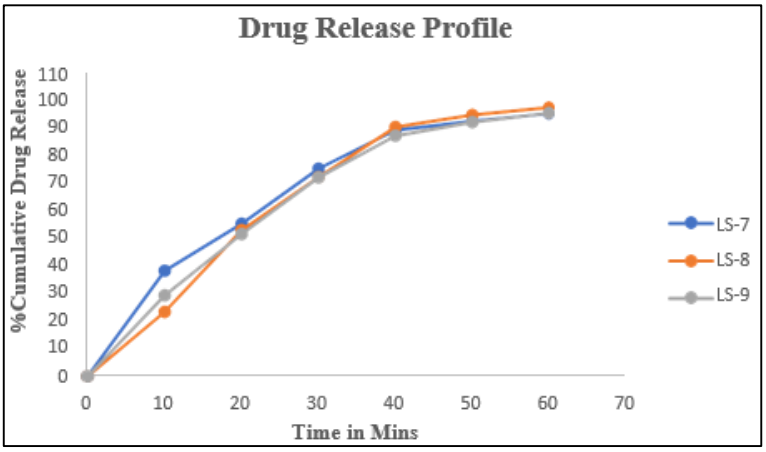

Fig 16: Graphical representation of *in-vitro* drug release profiles of LS-7, LS-8, LS-9

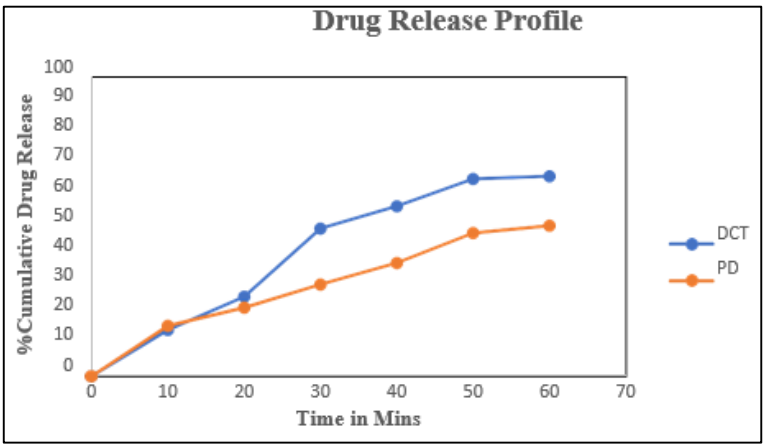

Fig 17: Graphical representation of *in-vitro* drug release profiles of dct and pure drug

Table 14: Comparison of % CDR of various formulations

Time (Mins)	%CDR of various formulations									
	LS-1	LS-2	LS-3	LS-4	LS-5	LS-6	LS-7	LS-8	LS-9	DCT
0	0	0	0	0	0	0	0	0	0	0
10	29.95	26.38	22.84	35.04	33.02	20.11	38.23	23.35	29.33	15.5
20	54.30	50.62	47.58	55.58	51.99	39.77	55.3	52.95	51.49	26.66
30	71.88	66.39	64.25	66.63	69.93	63.55	75.3	72.14	72.08	49.51
40	79.19	81.67	75.73	87.91	82.27	76.55	89.21	90.34	87.14	56.99
50	88.27	89.58	87.87	91.79	89.56	89.04	92.52	94.73	92.14	66.16
60	90.48	91.22	89.52	94.55	92.32	90.68	95.27	97.47	95.46	67.08

In-vitro release kinetics

Table 15: *In-vitro* release kinetics of optimized formulation (LS-8)

Time (mins)	Log Time	SQRT Time	% Cumulative Release	Log % Release	% Drug remaining	Log % Drug remaining
0		0	0		100	2
10	1.000	3.162	23.35	1.368	76.65	1.884
20	1.301	4.472	52.95	1.724	47.05	1.672
30	1.477	5.477	72.14	1.858	27.86	1.444
40	1.602	6.325	90.34	1.956	9.66	0.984
50	1.699	7.071	94.73	1.976	5.27	0.721

Table 16: Parameters for model fitting of optimized formulation (LS-8)

	Zero order	Peppas	Higuchi	First Order
K0(Slope)	1.687714	0.8088	6.651728323	-0.028
R2	0.9216	0.9478	0.9588	0.9755

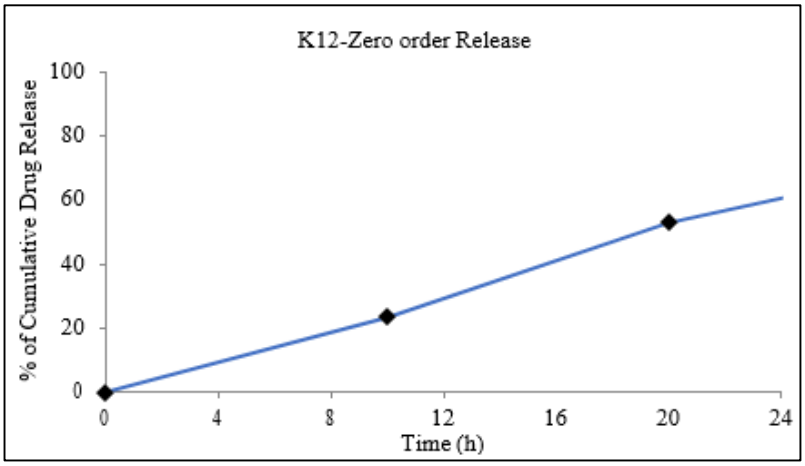

Fig 18: Graphical representation of zero order release from optimized formulation (LS-8)

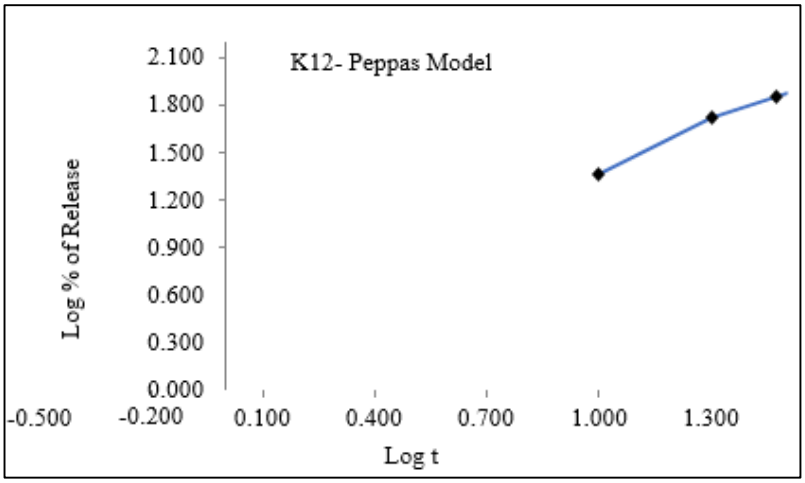

Fig 20: Graphical representation of drug release from optimized formulation (LS-8) by fitting into peppas model

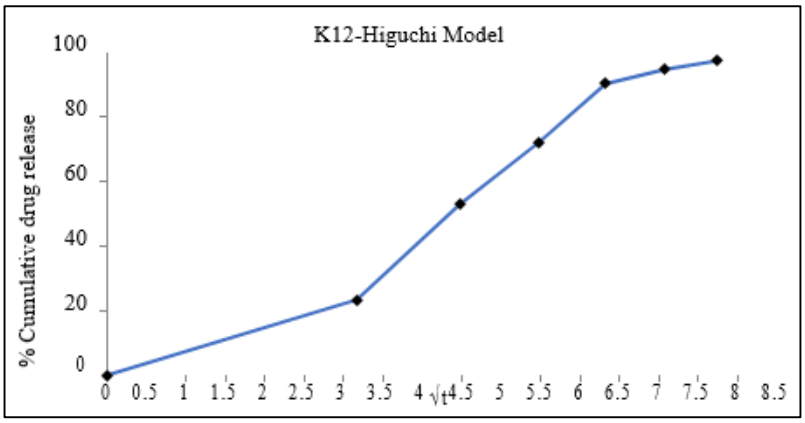

Fig 21: Graphical representation of drug release from optimized formulation (ls-8) by fitting into Higuchi model

Stability Studies

Table 17: Hardness data of the selected formulations kept for stability studies

Stability Condition	Formulations	Hardness (Kg/cm2)		
		No. of days		
		0	15	30
50C/ Ambient	LS-8	3.9±0.2	3.7±0.2	3.6±0.18
	DCT	4.5±0.34	4.5±0.15	4.3±0.15
250C/60%RH	LS-8	3.9±0.2	3.9±0.18	3.8±0.2
	DCT	4.5±0.34	4.4±0.06	4.4±0.15
400C/75%RH	LS-8	3.9±0.2	3.8±0.1	3.6±0.2
	DCT	4.5±0.34	4.3±0.15	4.2±0.14

Table 18: % Drug content for selected formulations kept for

Stability Condition	Formulations	Drug content (%)		
		No. of days		
		0	15	30
50C/ Ambient	LS-8	98.1±0.15	98.0±0.1	97.9±0.2
	DCT	98.5±0.3	98.3±0.87	98.3±0.37
250C/60%RH	LS-8	98.1±015	98.1±0.14	98.0±0.18
	DCT	98.5±0.3	98.4±0.75	98.2±0.28
400C/75%RH	LS-8	98.1±0.15	97.9±0.12	97.7±0.22
	DCT	98.5±0.3	98.2±0.43	98.0±0.33

Table 19: *In-vitro* disintegration data for selected formulations kept for stability studies

Stability Condition	Formulations	Disintegration time (%)		
		No. of days		
		0	15	30
50C/ Ambient	LS-8	255	254	252
	DCT	295	293	292
250C/60%RH	LS-8	255	255	251
	DCT	295	294	294
400C/75%RH	LS-8	255	253	250
	DCT	295	293	292

Table 20: *In-vitro* dissolution data for selected formulations kept for stability studies

Stability Condition	Formulations	% CDR		
		No. of days		
		0	15	30
50C/ Ambient	LS-8	97.47	97.44	97.41
	DCT	67.08	67.07	67.05
250C/60%RH	LS-8	97.47	97.42	97.40
	DCT	67.08	67.04	67.0
400C/75%RH	LS-8	97.47	97.41	97.38
	DCT	67.08	67.0	66.8

Similarity factor of %CDR for LS-8 between 0 days to 30 days was found to be 75.99

Discussion

Liquisolid technique is also known as powder solution technology. It is the technique which deals with the solubility enhancement of poorly soluble drugs. In the present investigation, an attempt was made to design and evaluate liquisolid tablets of Orlistat, a poorly soluble drug.

The new formulation technique of liquisolid was used to convert liquid medications such as solutions or suspensions of Orlistat in nonvolatile liquid vehicles, into acceptably flowing and compressible powders by blending with selective powder excipients. Several liquisolid tablet formulations were prepared using a new mathematical model to calculate the appropriate quantities of powder and liquid ingredients required to produce acceptably flowing and compressible admixtures. Various formulations were prepared and subjected to evaluation studies.

UV Spectrum OF Orlistat

Determination of λ max

A solution of 40µg/ml of Orlistat in methanol is scanned in the range of 200 to 400nm.

The drug exhibited a λmax at 202nm, and had good reproducibility. Fig No: 02

Standard Calibration curve of Orlistat in methanol

Table No. 5 shows the calibration curve data of Orlistat at 202 nm. Fig No: 3 shows the standard calibration curve with a regression value of 0.9962 and a slope of 0.0055 in methanol. The curve was found to be linear in the concentration range of 10- 100µg/ml.

Design and characterization of liquisolid tablets compatibility studies

Drug polymer compatibility studies were carried out using Fourier Transform Infra- Red spectroscopy to establish or rule out any possible interaction of Orlistat with the excipients used in the formulation. The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug and the data is given in the Table No: 6. The results indicated that the characteristic absorption peaks of pure Orlistat have appeared in the formulated tablets, without any significant change in their position, indicating no chemical interaction between orlistat and excipients. FT-IR spectrums are shown in Fig No: 4,5,6.

DSC Studies

The DSC thermograms show that the crystalline Orlistat was characterized by a single, sharp melting endothermic peak at 48.71^0C (Fig No: 7), which signifying the crystallinity of orlistat. The melting endotherm of the Orlistat in the liquisolid tablet (LS-8) was at 45 ^{0}C, whereas the disappearance of the sharp melting endothermic peak in the DSC scan of the formulation suggested that the drug has been converted to the amorphous form in the liquisolid formulation (Fig No: 8). These studies confirmed that there was no interaction between the drug and the excipients.

Solubility Studies in Various Non-Volatile Solvents

An ideal solvent was selected prior to the formulation by

carrying out solubility studies. The solubility of Orlistat in various non-volatile solvents namely, propylene glycol, polyethylene glycol 200, polyethylene glycol 400, and tween 80 was studied. The amount of drug dissolved in non-volatile solvents were shown in Table No: 7. The solubility studies indicated that, Orlistat has more solubility in Propylene glycol. Hence PG was selected as an ideal non-volatile solvent for the preparation of Orlistat liquisolid tablets.

Formulation of the Liquisolid Compacts

LS formulations of Orlistat were prepared by using non-volatile solvents, carrier materials like Avicel PH 102, coating material like Aerosil 200, and disintegrant like Sodium starch glycolate. A new mathematical model was applied to calculate the optimum quantities of carrier and coating materials to produce acceptably flowing and compressible powder blends. Directly compressed tablets of Orlistat were prepared by using the formula as shown in Table No: 03. Table No: 04 displays the experimental design and other variables like liquid load factor, amount of carrier and coating materials which were used to prepare the liquisolid tablets. Tablets were compressed into desired weight and thickness using circular 4 mm punches using rotary tablet compression machine.

Preliminary studies

The preliminary studies were carried out by preparing the formulations with similar conditions to avoid different process variables and subjecting the formulations to all pre-compression and post-compression parameters. The formulations were studied for the pre-compression parameters like bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio.

Then the prepared tablets were subjected to post compression tests like General appearance, size and shape, Weight variation, Tablet hardness, Friability, *In- vitro* disintegration test, *In-vitro* drug release and stability studies (As per ICH guidelines).

Study of carr's index and angle of repose values revealed that the powder mixture has good flow properties, which are the desirable characteristics of granules for further processing into tablets, all the pre-compression parameters have been given in Table No: 8. The tablets obtained were white colored with smooth texture.

Determination of thickness

The prepared formulations were evaluated for thickness and values were reported in Table No: 9 (Fig No: 09). It was found that all the tablets possessed uniform thickness with minor differences.

Determination of hardness

The tablets so prepared revealed good mechanical strength which was determined by Pfizer hardness tester and the values were recorded in Table No: 9 (Fig No: 10). Hardness so obtained is sufficient to withstand the conditions of mechanical stress during the manufacturing process.

Determination of friability

The tablets when subjected to Friability test revealed good mechanical strength. Friability was determined by using Lab India friability tester and the values were recorded in Table No. 9 (Fig No: 11). The values obtained for friability were within the limits, so the prepared tablets pass the friability test.

Determination of drug content

The prepared formulations were analyzed for drug content and the data is reported in Table No: 9 (Fig: 12). The drug content was found to be within 93.1 % to 98.1% which shows that the drug was uniformly distributed in all the formulations.

Determination of Weight Variation

The prepared formulations were analysed for average weight and the data was reported. The weight variation test was carried out as per the official procedure. The deviation from the mean was calculated and percentage deviation was found to be within limits.

***In-vitro* disintegration time**

The prepared tablets were analyzed for *in-vitro* disintegration time using DT apparatus and the data is reported in Table No: 9 (Fig No: 13). It was found that, the mean of the disintegration times for all the investigated tablets were less than 30 minutes, which fulfill the Pharmacopoeial requirements.

***In-Vitro* Dissolution Studies**

Orlistat was selected as the model drug for this study, since it is a slightly water-soluble substance and, thus an ideal candidate for testing the potential of rapid-release liquisolid compacts. The *in-vitro* release profiles of Orlistat from liquisolid compacts and directly compressed tablets were carried out using a dissolution test apparatus USP- type II. The dissolution study was carried out in 900 ml of 0.1N HCl and maintained at 37˚C ± 2˚C and 50 rpm. Then 5 ml of the samples were collected for up to 60 mins at

10 mins time intervals. The dissolution medium was replaced with 5 ml fresh dissolution fluid to maintain sink conditions. The *in-vitro* release profiles of the formulations were shown in Tables. Liquisolid compacts displayed more distinct *in-vitro* release characteristics than their directly compressed counterparts. The percentage drug release of LS-8 at the end of the 60th min was 97.47% and 67.08% for

DCT. It was confirmed that at 10 min LS-8 had the highest drug release of 23.35% compared with 15.5% for the directly compressed tablets (DCT). Since the liquisolid compacts contain a solution of the drug in non-volatile vehicle, the drug surface available for dissolution is tremendously increased. In essence, after disintegration, the liquisolid primary particles suspended in the dissolving medium contains the drug in a molecularly dispersed state, whereas the directly compressed compacts are merely exposed micronized drug particles. Therefore, in the case of liquisolid compacts, the surface area of drug available for dissolution is much greater than that of the directly compressed compacts. According to the classic dissolution equation i.e., Noyes

Whitney equation ($DR = (D/h)\ S\ (CS - C)$. The drug dissolution rate (DR) of a drug is directly proportional to its concentration gradient $(CS - C)$ in the stagnant diffusion layer and its surface (S) available for dissolution. CS is the saturation solubility of the drug in the dissolution medium and thus, it is a constant characteristic property related to the drug and dissolving liquid involved. Since all of the dissolution tests for formulations were done at a constant rotational paddle speed (50 rpm) and identical dissolving media, we can assume that the thickness (h) of the stagnant

diffusion layer and the diffusion coefficient (*D*) of the drug molecules remain almost identical. Therefore, the observed higher dissolution rates of Orlistat from liquisolid tablets are due to the significantly increased surface of the molecularly dispersed Orlistat.

Microcrystalline cellulose was used as a carrier material, which has disintegration property, which could facilitate disintegration of granules and improve the dissolution of Orlistat. Because of the presence of a non-volatile solvent, as a binding agent in the liquisolid formulation, delayed disintegration time is expected. However, in the liquisolid granules containing microcrystalline cellulose, a fast disintegration of granules occurred which can be explained by the disintegrating property of microcrystalline cellulose. Some of the additives like PVP, HPMC and HPG were incorporated in the formulations LS-7, LS-8 and LS-9 respectively, to improve further dissolution. Liquisolid tablets containing additives showed improved dissolution. Formulation LS-8 containing HPMC showed the maximum drug release compared to other formulations, due to its dissolution enhancing property, so LS-8 is considered as the optimized formula. Comparative drug release profiles have been shown in Fig No: 14, 15, 16 and Table No: 14.

IN-Vitro drug release kinetics

The drug release mechanism was analysed by fitting the release data into various models such as zero order, first order, Higuchi and Korsmeyer-Peppas. The results were compiled in Table No:15, 16. The percentage drug release with data fitting to various kinetic models for the optimised formulation is presented in Fig No: 18,19, 20, 21.

It was observed that the r2 values of First order kinetics were close to 1, the drug release follows the First order as the main mechanism of drug release from the formulation. Further, the observed diffusion coefficient values are indicative of the fact that drug release from the formulation follows Non-Fickian transport mechanism.

Stability Studies

The selected formulation was subjected for stability studies based on their drug content and *in-vitro* drug release characteristics. The stability data in Table No: 17, 18, 19, and 20 showed that there were no changes in the appearance of the tablets indicating that the formulations were stable at all the conditions to which they were exposed. It was observed that there was slight reduction in the drug content of the tablets which were stored at 40 0C / 75% RH at the end of 30 days and no significant change in drug content were observed for formulations stored at room temperature and at 5 ^{0}C. *In-vitro* drug dissolution studies for two formulations were carried out at 0, 15 and 30 days and did not reveal any significant change in drug release from all the formulations. Similarity factor of %CDR for LS-8 between 0 days to 30 days was found to be 75.99. Thus, over all we may conclude that, the drug is stable throughout the storage period.

Conclusion

In the present work, liquisolid tablets were prepared to improve the dissolution profile of the poorly water soluble drug. Orlistat Liquisolid tablets were prepared by using Avicel PH 102 as carrier and Aerosil as coating material along with propylene glycol as a non-volatile solvent.

From the FT-IR spectroscopic study it was observed that there was no significant shift in the IR values. Hence it may be concluded that there was no chemical interaction between the drug and the excipients. All the formulations were subjected to pre- formulation studies like Carr's index, Hausner's ratio and Angle of repose. The values were within the acceptable range. All the post compression studies like hardness, friability, weight variation, thickness measurement, disintegration time and drug content indicated that the values were within the acceptable range.

DSC studies indicated the conversion of crystalline form of the drug to amorphous form during the formulation, absence of crystallinity helps in solubilization, which further improves the dissolution rate. By considering pre-compression and post- compression evaluation parameters, LS-8 made with Propylene glycol and HPMC as adjuvant proved to be the optimized formula.

Results suggest that liquisolid technique is a promising alternative technique to increase the rate of dissolution of water insoluble drugs. Orlistat can be successfully formulated as liquisolid tablets to improve dissolution rate and thus the bioavailability.

Summary

The liquisolid technique can be an effective method for enhancing the rate of dissolution of water insoluble drugs such as Orlistat. As compared to conventional directly compressed tablets, the liquisolid compacts of Orlistat significantly enhances *in-vitro* release properties due to increased wetting and surface area of drug available for dissolution. This novel formulation approach may be helpful in improving oral bioavailability.

Orlistat liquisolid tablets were prepared by using Avicel PH102 as carrier, Colloidal silica (Aerosil) as coating material and Propylene glycol as the liquid vehicle of choice, which may produce Orlistat liquisolid compacts with maximum drug dissolution rate. Various liquisolid tablets were prepared by adding some of the additives like PVP, HPMC and HPG to enhance dissolution characteristics. Liquisolid tablets containing propylene glycol as a non-volatile solvent and HPMC as an additive showed better drug release profiles at the end of 60 minutes. By considering other pre-compression and post-compression evaluation parameters, LS-8 was concluded as the optimized formula.

The use of nonvolatile solvent in the formulation causes increased wettability of water insoluble drugs and ensures molecular dispersion of drug in the formulation. The enhanced rate of drug dissolution from liquisolid tablets was probably due to an increase in wetting properties and surface area of drug particles available for dissolution and therefore, they show improved release rates and hence may be greater bioavailability.

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