FORMULATION AND *INVITRO* EVALUATION OF ORLISTAT SOLID DISPERSION

G. Bhagya Buela[1*], Amatul Noor Shaima[2], Bibi Ayesha Farha[2], Shareef Unnisa Begum[2], Mariya Mehveen[2], Mr. V. Vijaya Kumar[3]

Article History: **Received:** 28.05.2023 **Revised:** 22.06.2023 **Accepted:** 19.07.2023

Abstract

Objectives: orlistat is used as an antiobesity drug, widely used orally in the treatment of hypercolestremia. The model drug belongs to BCS class II and undergoes extensive first-pass metabolism with a bioavailability of only about 15%. Hence this work was planned to improve the oral bioavailability of orlistat by increasing its solubility and dissolution characteristics through the solid dispersion technique using HPMC, PEG 4000 and Eudragit L 100 as carriers.

Methods: Solid binary systems of orlistat were prepared by solvent evaporation method using HPMC, PEG and Eudragit L 100 as carriers and in the ratios of drug and polymer (1:1, 1:2 and1:3). The various formulations were characterized by drug content, FT-IR, XRD and *in vitro* dissolution test using USP dissolution test apparatus Type I (basket method) in dissolution medium of 0.1N HCl. The *in vitro* dissolution results of all preparations were computed by using dissolution software PCP DISSO V3.

Results: The percentage Solubility of the drug in different solvents after 24hrs Results was revealed that the pure drug Orlistat was freely soluble in chloroform and insoluble in water. Melting point of the pure drug was found to be 40- 480C. It shows that the pure drug unstable at higher temperatures. Derived properties were performed for pure drug. Results show that the drug compiles with the IP specifications. FT-IR spectra was taken for solid dispersion containing HPMC, PEG4000 and Eudragit L 100 compared with pure drug FTIR data. which reveal that there were no interaction between the pure drug and excipients. The data obtained for *in-vitro* release were fitted into equations for the zero order and first order, Higuchi, and Korsmeyer, release models; the interpretation of the data was based on the value of the resulting regression co-efficient.

Conclusions: Orlistat solid dispersions were prepared using HPMC, PEG, and Eudragit L100 as Carriers to improve physicochemical characteristics of orlistat. Solid dispersion technique found to be effective in increasing the aqueous solubility of orlistat. In - vitro dissolution studies showed that in dispersion systems containing HPMC, Eudragit L100, and dissolution were retarded, which attributed to ionic interaction and gel forming respectively but solid dispersion containing PEG 4000, as a carrier, gave faster dissolution rates than the physical mixture. Finally, solid dispersions of orlistat: PEG 4000 (OP-SD3) prepared in ratio 1:3 showed excellent physicochemical characteristics and was found to be described by the first order kinetic, and was selected as the best formulation in this study. Thus the solid dispersion technique found to be effective in increasing aqueous solubility of orlistat.

Keywords: orlistat; solid dispersion etc.

[1*]Asst professor, Department of Pharmaceutics, Shadan Women,s College of Pharmacy, Raj Bhavan rd, taj enclave Khairtabad, Hyderabad, Telangana-500004.
[2]Department of Pharmaceutics, Shadan Women,s College of Pharmacy, Raj Bhavan rd, taj enclave Khairtabad, Hyderabad, Telangana-500004.
[3]Asst.Professor, Department of Pharmaceutics, School of pharmacy, Sathyabama Institute of Science and Technology, Chennai.

***Corresponding Author:** G. Bhagya Buela
*Asst professor, Department of Pharmaceutics, Shadan Women,s College of Pharmacy, Raj Bhavan rd, taj enclave Khairtabad, Hyderabad, Telangana-500004.

DOI: 10.48047/ecb/2023.12.si10.00286

INTRODUCTION

Drug solubility

Solubility enhancement of poorly water-soluble drugs is a crucial issue to improve their solubility and bioavailability. . It is observed 40 percent of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. Such compounds are very challenging for formulation scientists in developing bioavailable dosage forms. Poorly water soluble compound has classically been defined as one dissolving in less than 1 part per 10000 part of water[1]. A poorly water soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract[2]. Thus a greater understanding of dissolution and absorption behaviors of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products. Consideration of the modified Noyes–Whitney equation[3] provides some hints as to how the dissolution rate of poorly soluble compounds might be improved to minimize the limitations to oral bioavailability.

$$\frac{dc}{dt} = (C_s - C)\frac{KDS}{Vh} \quad \ldots 1$$

where dc/dt is the rate of increase in concentration: C is the concentration of drug in a bulk solution in which dissolution of the solid particles is taking place; K is proportionality constant: D is the diffusion coefficient of the drug in the solvent; S is surface area; h is the thickness of the diffusion layer around a particle and Cs is the solubility of the drug in the solvent. If we consider a given drug under well defined conditions (such as controlled liquid intake), we may assume that D, V and h are relatively constant values. Thus, we can reduce equation (1) to:

$$\frac{dc}{dt} = KS(C_s - C) \quad \ldots 2$$

Equation (2) shows that the two variables, which may be controlled by the formulation, are the surface area and the solubility of the drug. These two variables can be altered by the following techniques:

1. Control the solubility of a weak acid or base by buffering the entire dissolution medium the “microenvironment” of the diffusion layer surrounding a particle.
2. Control the solubility of the drug through choice of the physical state, such as crystal form, its hydrate and its amorphous form.
3. Determine the surface area of the drug through control particle size[4].

METHODS

Development of UV spectroscopic method

To prevent the photo degradation of orlistat, all the experimental work was carried out under light protected conditions.

Determination of absorption maxima: Absorption maxima are the wavelength at which absorption takes place. For accurate analytical work it is important to determine the absorption maxima of the substance under study. 100 mg of orlistat was dissolved in 100 ml of methanol. 1ml of this solution was pipetted out in a series of volumetric flask and diluted serially with 0.1N HCl (pH 1.2) to get desired concentration and subjected for UV scanning in the range of 200-800 nm using double beam UV-VIS spectrophotometer (pharmaspec1700, Shimahdzu, Japan). The absorption maxima for orlistat were obtained at 254 nm with a characteristic peak.

Preparation of calibration curve: Using absorption maxima a standard curve was prepared in the concentration range of 2-10 µg/ml. For the preparation of calibration curve, stock solution was prepared by dissolving 100 mg of accurately weighed orlistat in 100 ml of methanol. Further 1 ml of this solution was pippeted into 100 ml of volumetric flask and diluted to 100 ml with methanol. From this, 2, 4, 6, 8 and 10 ml pipetted into a series of 10 ml volumetric flask and volume was made up to 10 ml with 0.1N HCl to get 2, 4, 6, 8 and 10 µg/ml of orlistat respectively. The optical density values of resulting solutions were measured at 254 nm in double beam UV-VIS spectrophotometer (pharmaspec-1700, Shimadzu, Japan) and statistical data is given in **table 4.** The concentration versus optical density values are plotted and shown in the **figure 1** [59]**.**

Preparation of calibration curve: 100 mg of accurately weighed orlistat in 100 ml of methanol. Further 1 ml of this solution was pippeted into 100 ml of volumetric flask and diluted to 100 ml with phosphate buffer of 0.1N HCl. From this, 2, 4, 6, 8 and 10 ml pipetted into a series of 10 ml volumetric flask and volume was made up to 10 ml with 0.1N HCl to get 2, 4, 6, 8 and 10 µg/ml of orlistat respectively. The optical density values of resulting solutions were measured at 254 nm in double beam UV-VIS spectrophotometer (pharmaspec-1700, Shimadzu, Japan) and statistical data is given in **table 4.** The concentration versus optical density values are plotted and shown in the **figure 1** [60]**.**

COMPATIBILITY STUDIES FOR PHYSICAL MIXTURES:

FT-IR spectrophotometer were using for the compatibility studies between drug and polymer . The spectra were recorded for orlistat, PEG 4000 ,HPMC, and Eudragit L 100 physical mixtures . The samples were prepared by the potassium bromide (KBr) disc method. The KBr discs were prepared by compressing the powder and scanning range was kept from 4000 to 450 cm−1.

METHOD OF PREPARATION:

Preparation of physical mixture:

Drug and carrier were weighed in the ratio of 1:1, 1:2 and 1:3. The physical mixture was prepared by mixing drug and carrier in a mortar. Solid mass was pulverized and passed through sieve no.80 to get uniform sized particles.

Materials:

1. orlistat
2. Polyethylene glycol-4000
3. hydroxy propyl methyl cellulose
4. Eudragit L100.

Table5. Formulation Table of physical mixture

S.No	Formulation Code	Drug : Polymer	Drug (mg)	Polymer (mg)
1	OH:PM1	1:1	100	100
2	OH:PM2	1:2	100	200
3	OH:PM3	1:3	100	300
4	OP:PM1	1:1	100	100
5	OP:PM2	1:2	100	200
6	OP:PM3	1:3	100	300
7	OE:PM1	1:1	100	100
8	OE:PM2	1:2	100	200
9	OE:PM3	1:3	100	300

II. Preparation of Solid Dispersion:

9 formulations of solid dispersions containing orlistat with HPMC, PEG 4000 and Eudragit L 100 as a carrier in the ratios of 1; 1, 1; 2, 1:3 were prepared by dispersion method in a mortar and pestle. Then to that powder add suitable solvent in which the powder was completely soluble. Heat the solution till all the solvent gets evaporated leaving a clear solvent free film of residue at the bottom of the china dish. The film was further dried to get the constant weight and then subjected to evaluation tests. In this present study nine formulations of orlistat dispersions were prepared using varying proportions of HPMC, PEG 4000 and Eudragit L100 [61].

Materials:

1. orlistat
2. Polyethylene glycol-4000
3. hydroxy propyl methyl cellulose
4. Eudragit L100.
5. Methanol.

Table6. Formulation Table of solid dispersion

S.No	Formulation code	Drug : Polymer	Drug (mg)	Polymer (mg)
1	OH:SD1	1:1	100	100
2	OH:SD2	1:2	100	200
3	OH:SD3	1:3	100	300
4	OP:SD1	1:1	100	100
5	OP:SD2	1:2	100	200
6	OP:SD3	1:3	100	300
7	OE:SD1	1:1	100	100
8	OE:SD2	1:2	100	200
9	OE:SD3	1:3	100	300

EVALUATION OF ORLISTAT SOLID DISPERSION SYSTEMS:

I. Solubility studies [62]: The solid dispersions, physical mixtures and pure drug saturation solubility were performed by weighed amount of orlistat pure drug, physical mixture and all prepared solid dispersions equivalent to 40mg of the drug, dispersed in 25ml vials containing 15ml of distilled water. The sealed vials were shaken on rotary shaker for 24 hrs at room temperature and equilibrated for 48 hrs. An aliquot was passed

through 0.45µ nylon disc filter and the filtrate was suitably diluted and analyzed on UV at 254nm.

II. Drug content uniformity : In each case PMs and solid dispersion system, sample equivalent to 40 mg of orlistat was accurately weighed and transferred to 100 ml volumetric flask and extracted in methanol. The volume was made up to 100 ml with methanol. From this 1ml is subsequently diluted to 10 ml with methanol and assayed for orlistat content by measuring at 254nm using methanol as blank. The orlistat content was calculated from the calibration curve. The experiments were conducted in triplicate.

III. X-Ray Diffraction Studies:
Decrease in crystallinity of the drug is often a predominant mechanism responsible for increased dissolution rates. The X-ray diffraction (XRD) analysis was carried out to evaluate possible reduction in crystallinity of orlistat after formulation into solid dispersions with the polymers selected batches of the solid dispersions were subjected to powder XRD using the copper K-α radiation generated at 20mA and 40 KV potential. The diffracted X-rays were then detected in the 2φ range of 5-70º, and the results processed by a pre-loaded computer program.

IV. *In Vitro* Drug Release Studies:
The dissolution process is carried in USP Type I apparatus (basket apparatus). Accurately weigh 100mg of the product and dropped in 900ml of 0.1N Hcl maintained at a temperature of 37ºC ± 0.5oC and stirred at a speed of 75 rpm. At different time intervals a 5ml aliquot of the sample withdrawn and the same volume was replaced with an equal amount of plain dissolution medium. The collected samples are analyzed the λmax 254nm using UV Visible spectrophotometer against the medium buffer as a blank.

RESULTS AND DISCUSSION

Results: Table 7: Calibration curve data of orlistat in methanol.

Sl. No.	Concentration (mcg/ml)	Absorbance (nm) ± SD
0	**0**	**0**
1	**2**	**0.067±0.04**
2	**4**	**0.136±0.05**
3	**6**	**0.21±0.05**
4	**8**	**0.283±0.06**
5	**10**	**0.358±0.08**

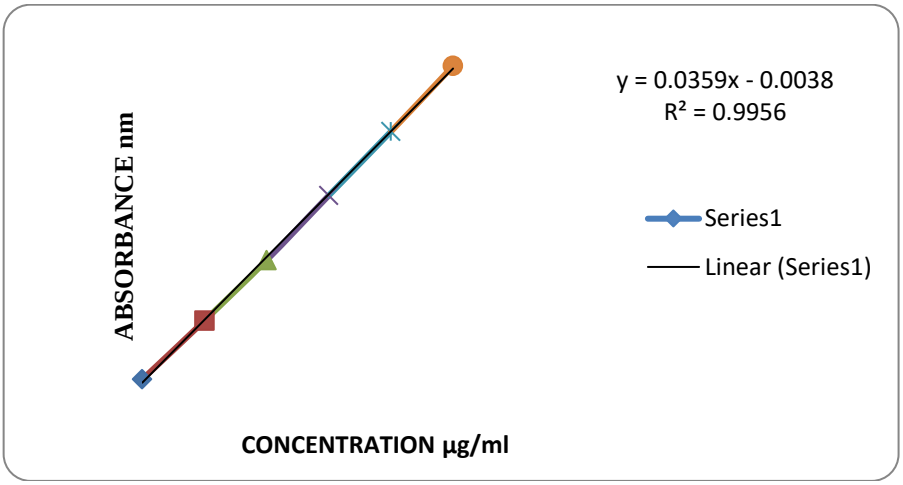


Figure 3: Calibration curve of orlistat in methanol

Table 8: Calibration curve data of orlistat in 1.2 pH acetic buffer.

Sl. No.	Concentration (mcg/ml)	Absorbance (nm) ± SD
0	**0**	**0**
1	**2**	**0.099±0.03**
2	**4**	**0.204±0.06**
3	**6**	**0.311±0.03**
4	**8**	**0.405±0.04**
5	**10**	**0.507±0.07**

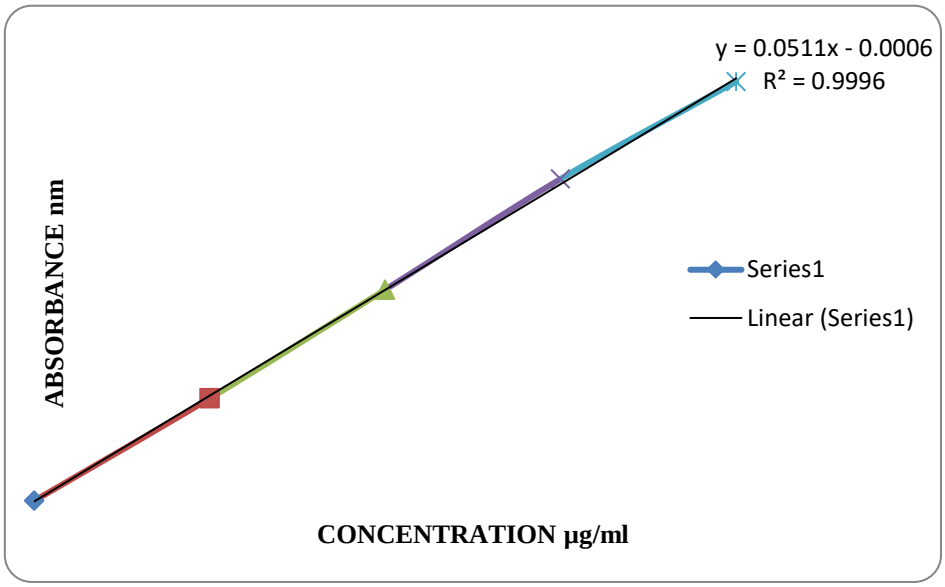


Figure 4: Calibration curve of orlistat in acetic buffer pH 1.2.

Table 9: Solubility Data of Physical Mixture and Solid Dispersion

Carrier	Code	Drug/Carrier Ratio	Mean Absorbance± SD	Concentration (µg/ml)
HPMC	OH:PM1	1:1	0.534±0.05	5.93
	OH:PM2	1:2	0.585±0.06	6.50
	OH:PM3	1:3	0.725±0.03	8.06
PEG4000	OP:PM1	1:1	0.741±0.03	8.59
	OP:PM2	1:2	0.781±0.04	9.36
	OP:PM3	1:3	0.656±0.05	10.37
EUDRAGIT L 100	OE:PM1	1:1	0.773±0.04	8.23
	OE:PM2	1:2	0.842±0.02	8.67
	OE:PM3	1:3	0.934±0.06	7.29
HPMC	OH:SD1	1:1	0.689±0.03	7.66
	OH:SD2	1:2	0.705±0.02	7.83
	OH:SD3	1:3	0.762±0.08	8.47
PEG 4000	OP:SD1	1:1	0.799±0.06	9.67
	OP:SD2	1:2	0.813±0.04	10.36
	OP:SD3	1:3	0.849±0.07	10.99
EUDRAGIT L 100	OE:SD1	1:1	0.870±0.08	8.88
	OE:SD2	1:2	0.932±0.06	9.03
	OE:SD3	1:3	0.989±0.04	9.43

Table 10: Orlistat drug content in Physical mixture and all solid dispersion systems

Code	Amount of drug taken	Amount of drug recovered mean ± SD	% drug content mean ± SD
OH:PM1	40mg	38.8±0.2082	97.08±0.5204
OH:PM2	40mg	39.7±0.2517	99.4±0.6557
OH:PM3	40mg	39.4±0.6557	98.46±1.662
OP:PM1	40mg	39.3±0.3512	98.4±0.854
OP:PM2	40mg	39.9±0.4041	99.8±1.015
OP:PM3	40mg	39.5±0.6658	98.81±1.643
OE:PM1	40mg	39.3±0.2517	98.3±0.655
OE:PM2	40mg	39.3±0.3512	98.41±0.878
OE:PM3	40mg	38.9±0.1000	97.91±1.337
OH:SD1	40mg	39.0±0.3055	97.5±0.866
OH:SD2	40mg	39.2±0.5508	98.06±1.401
OH:SD3	40mg	39.4±0.5508	98.65±1.376
OP:SD1	40mg	39.1±0.6033	97.3±1.329
OP:SD2	40mg	39.3±0.6753	98.4±0.854
OP:SD3	40mg	39.7±0.3215	97.9±0.531
OE:SD1	40mg	38.9±0.1000	97.91±1.337
OE:SD2	40mg	38.7±0.6110	98.3±1.439
OE:SD3	40mg	39.6±0.5518	99.4±0.6566

Fig 5 : FT–IR spectra of orlistat pure drug

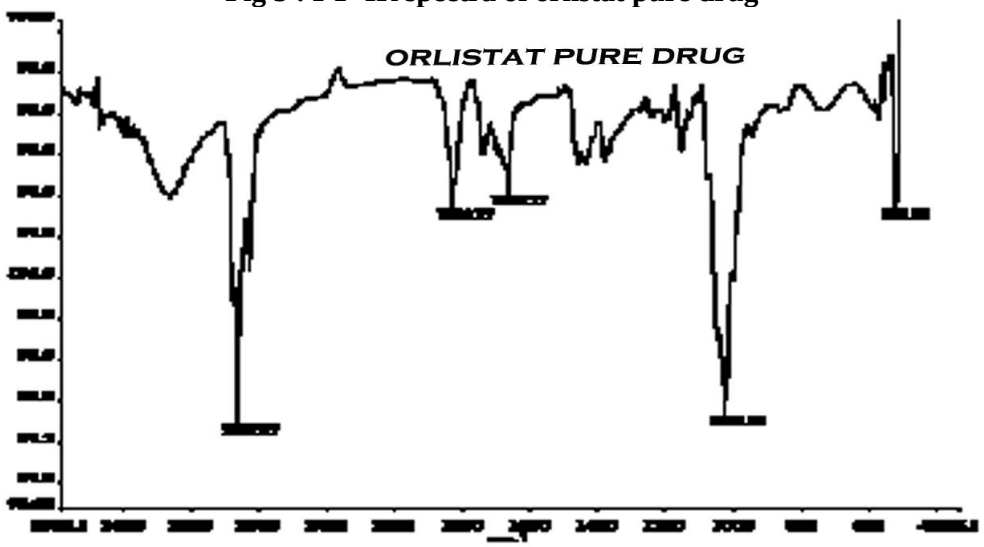


Fig 6 : FT–IR spectra of orlistat with HPMC Physical Mixture

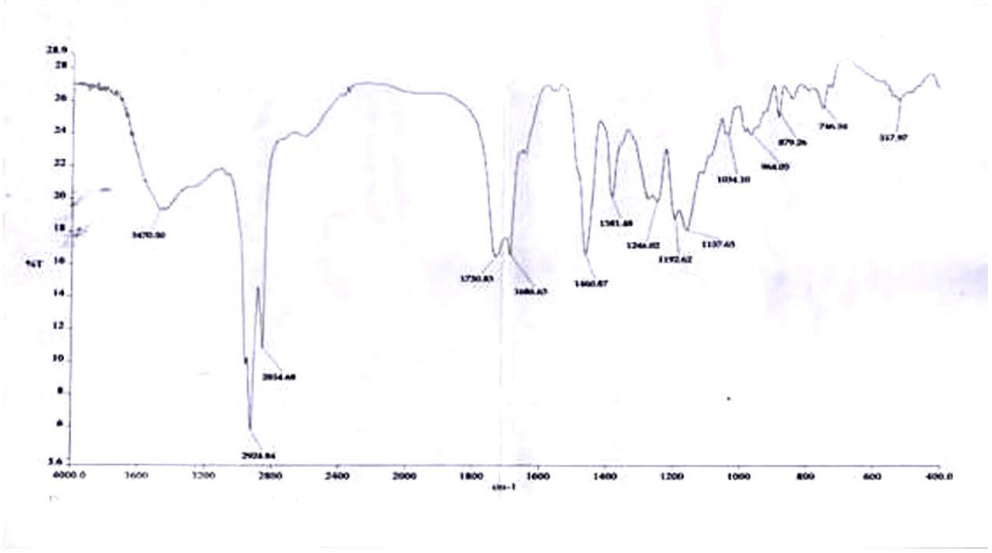


Fig 7 : FT–IR spectra of orlistat with PEG 4000 Physical Mixture

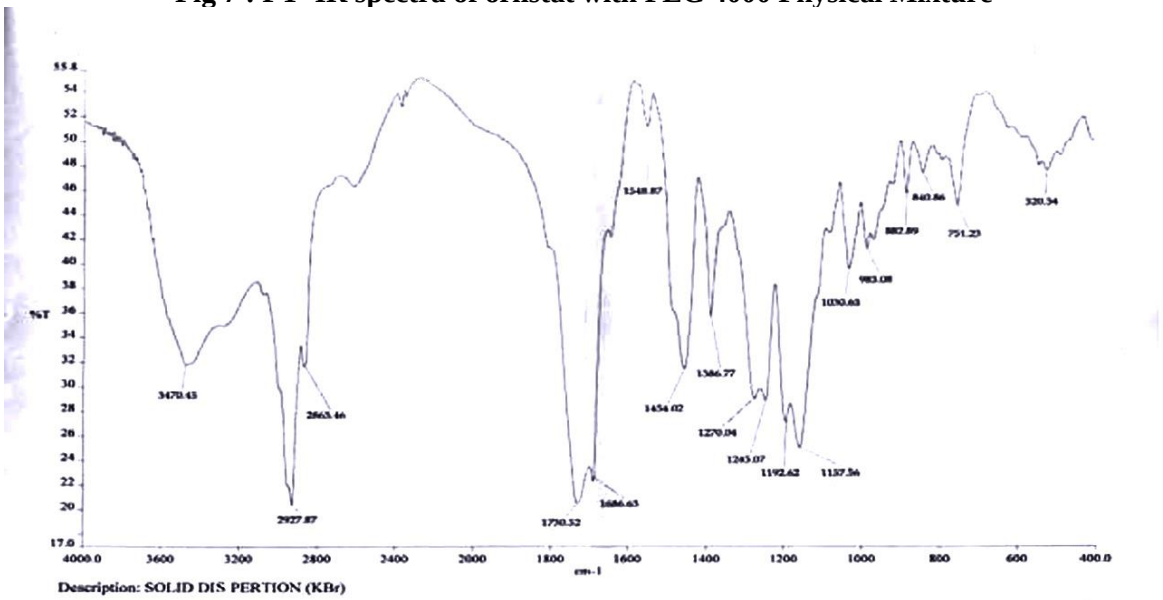


Fig 8: FT–IR spectra of orlistat with Eudragit L 100 Physical Mixture

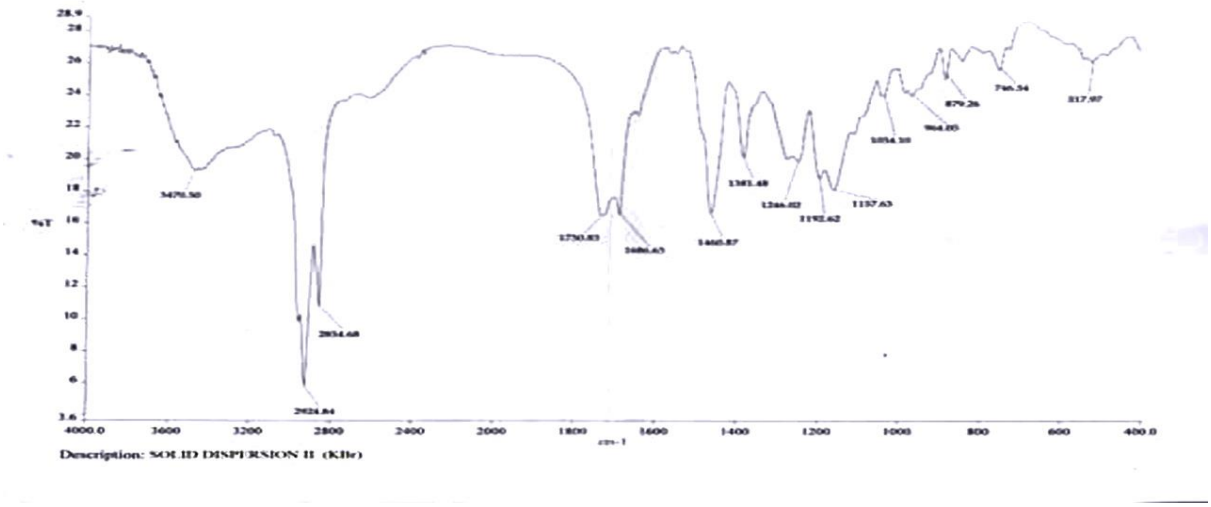


Fig 9: FT–IR spectra of orlistat with PEG 4000 Solid Dispersion(1:3)

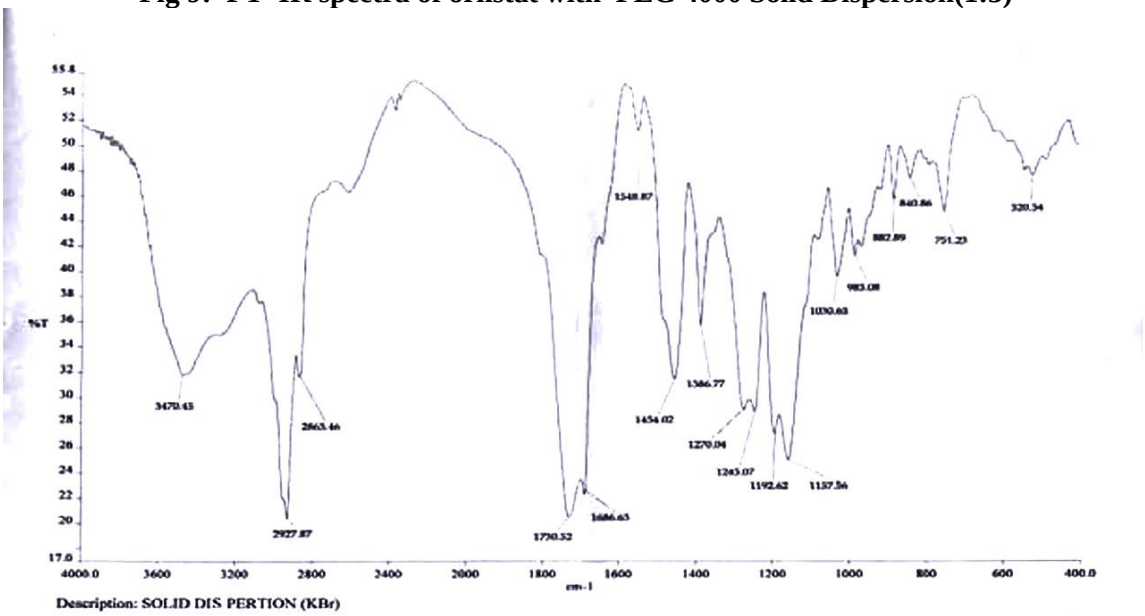


Fig 10: X-Ray Diffractogram of Orlistat Pure Drug

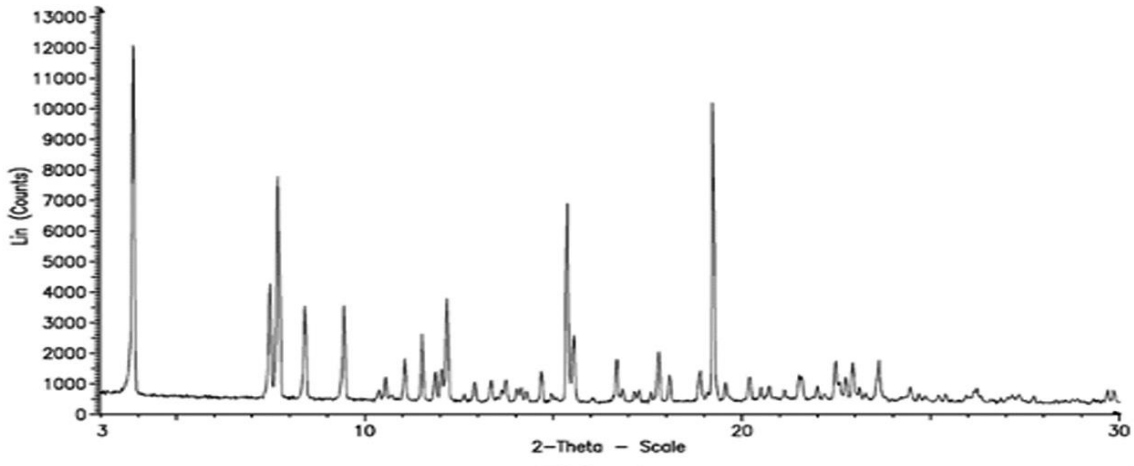


Fig 11: X-Ray Diffractogram of Orlistat Solid Dispersion with HPMC

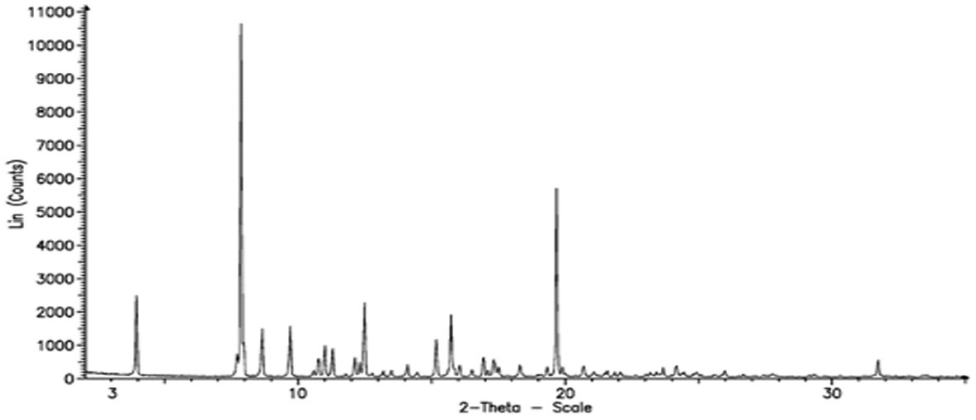


Fig 12: X-Ray Diffractogram of Orlistat Solid Dispersion with PEG 4000

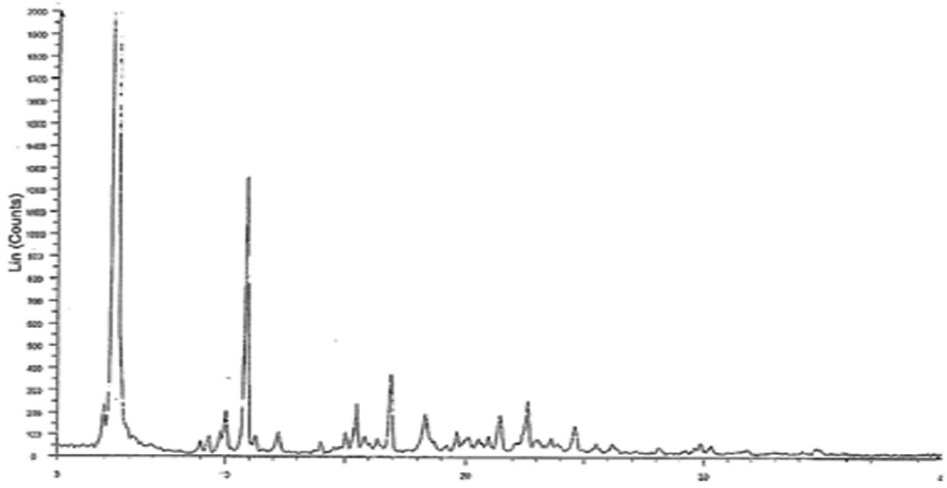


Fig 13: X-Ray Diffractogram of Orlistat Solid Dispersion with Eudragit L 100

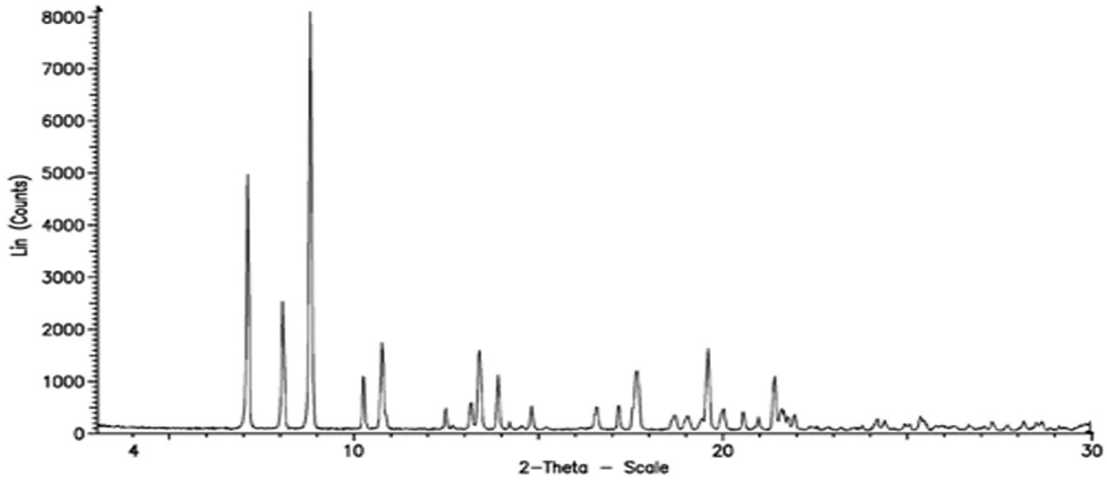


Table 11 : *In vitro* Drug Release Data of Orlistat from various HPMC Physical Mixtures

	Cumulative Percent Drug Released (±SD)				Percentage Drug Remaining				Log Percent Drug Remaining			
	Pure drug	OH -PM1	OH –PM2	OH –PM3	Pure drug	OH- PM1	OH- PM2	OH -PM3	Pure drug	OH- PM1	OH- PM2	OH-PM3
0	0	0	0	0	0	0	0	0	0	0	0	0
5	1.09 ± 0.03	2.25±0.03	2.53±0.01	2.44±0.01	98.91	97.75	97.47	97.56	1.995	1.990	1.988	1.989
10	2.57 ± 0.01	2.97±0.01	4.05±0.01	3.3±0.02	97.43	97.03	95.95	96.7	1.988	1.986	1.982	1.985
15	3.15 ± 0.01	4.68±0.12	6.89±0.17	5.85±0.6	96.85	95.32	83.11	94.15	1.986	1.979	1.968	1.973
30	7.03 ± 0.02	8.1±0.13	11.44±0.25	9.72±0.8	92.97	91.9	88.0	90.28	1.968	1.963	1.944	1.955
45	10.22 ± 0.06	13.14±0.15	17.74±1.01	15.48±1.01	87.78	86.86	82.26	84.52	1.953	1.938	1.915	1.926
60	13.38 ± 0.01	19.62±1.1	17.92±1.4	22.92±1.2	86.62	80.38	82.08	77.08	1.937	1.905	1.914	1.886
90	18.94 ± 0.01	27.81±1.3	18.81±1.6	30.81±1.9	81.06	72.19	81.19	69.19	1.908	1.858	1.909	1.840
120	22.19 ± 0.02	38.80±2.1	29.80±1.8	46.80±2.4	77.81	61.2	70.2	53.2	1.891	1.786	1.846	1.725

OH:PM1 Orlistat – HPMC Physical Mixture(1:1)
OH:PM2 Orlistat – HPMC Physical Mixture(1:2)
OH:PM3 Orlistat – HPMC Physical Mixture(1:3)

Fig 13: *In vitro* Release Plots of Orlistat Pure Drug and its Physical Mixture prepared with HPMC

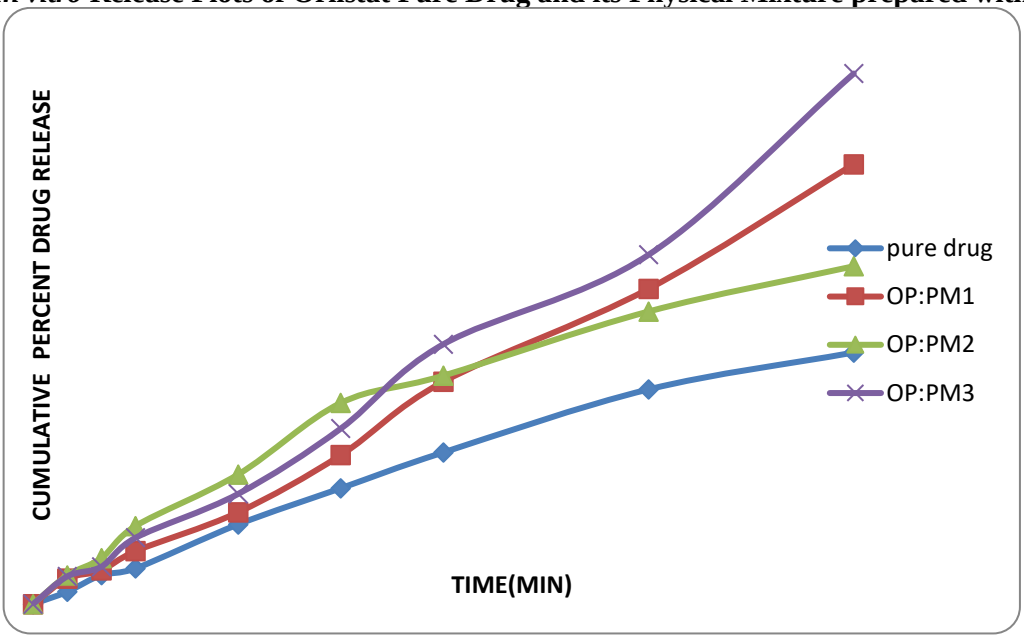


Table 12: *In vitro* Drug Release Data of Orlistat from various PEG-4000 Physical Mixtures

Time (min)	Cumulative Percent Drug Released (±SD)				Percentage Drug Remaining				Log Percent Drug Remaining			
	Pure drug	OP -PM1	OP –PM2	OP –PM3	Pure drug	OP-PM1	OP-PM2	OP–PM3	Pure drug	OP-PM1	OP-PM2	OP-PM3
0	0	0	0	0	0	0	0	0	0	0	0	0
5	1.09 ± 0.03	1.35±0.05	1.53±0.45	1.87±0.4	98.91	98.65	98.47	98.13	1.995	1.994	1.993	1.991
10	2.57 ± 0.01	2.87±0.06	3.05±0.1	3.23±0.1	97.43	97.13	96.95	96.77	1.988	1.987	1.986	1.985
15	3.15 ± 0.01	6.18±0.1	7.85±0.8	7.65±0.8	96.85	93.82	92.15	92.35	1.986	1.972	1.964	1.965
30	7.03 ± 0.02	11.1±0.7	12.44±0.9	13.77±1.6	92.97	88.9	81.56	86.23	1.968	1.948	1.942	1.935
45	10.22 ± 0.06	17.54±0.6	20.74±1.01	21.96±1.9	89.78	82.46	79.26	78.04	1.953	1.916	1.899	1.892
60	13.38 ± 0.01	26.02±1.1	29.52±1.1	31.05±1.7	86.62	73.98	70.48	68.95	1.937	1.869	1.848	1.838
90	18.94 ± 0.01	37.81±1.8	40.86±1.13	43.81±1.9	81.06	62.19	59.14	56.19	1.908	1.793	1.771	1.749
120	22.19 ± 0.02	49.80±2.4	54.54±2.07	58.24±2.4	77.81	50.2	45.46	41.76	1.891	1.700	1.647	1.620

OP:PM1 Orlistat – PEG 4000 Physical Mixture(1:1)
OP:PM2 Orlistat – PEG 4000 Physical Mixture(1:2)
OP:PM3 Orlistat – PEG 4000 Physical Mixture(1:3)

Figure-15: *In vitro* Release Plots of Orlistat Pure Drug and its Physical Mixture prepared with PEG 4000

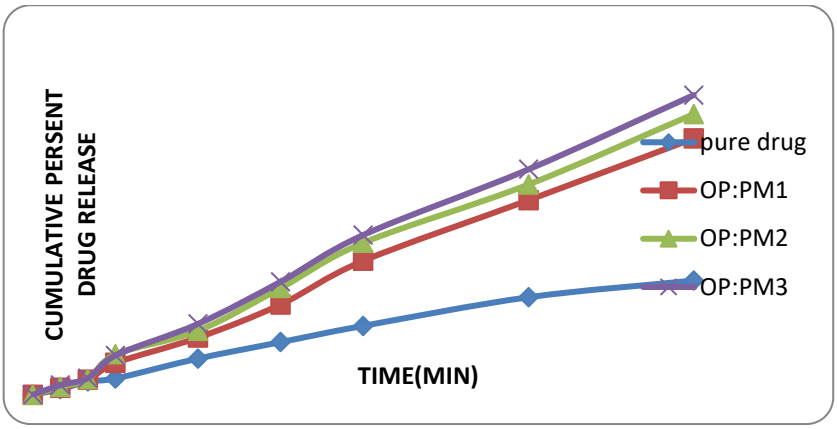


Table 13 : *In vitro* Drug Release Data of Orlistat from various Eudragit L 100 Physical Mixtures

Time (min)	Cumulative Percent Drug Released (±SD)				Percentage Drug Remaining				Log Percent Drug Remaining			
	Pure drug	OE-PM1	OE-PM2	OE-PM3	Pure drug	OE-PM1	OE-PM2	OE-PM3	Pure drug	OE-PM1	OE-PM2	OE-PM3
0	0	0	0	0	0	0	0	0	0	0	0	0
5	1.09 ± 0.03	1.35±0.05	1.13±0.35	1.07±0.2	98.91	98.65	98.87	98.93	1.995	1.994	1.995	1.995
10	2.57 ± 0.01	3.07±0.06	2.43±0.1	1.97±0.1	97.43	96.93	97.57	98.03	1.988	1.986	1.989	1.991
15	3.15 ± 0.01	6.12±0.1	5.4±0.8	4.65±0.7	96.85	93.88	94.6	95.35	1.986	1.972	1.975	1.979
30	7.03 ± 0.02	10.43±0.7	10.26±0.9	8.91±1.6	92.97	89.57	89.74	91.09	1.968	1.952	1.952	1.959
45	10.22 ± 0.06	19.54±0.6	17.82±1.01	17.96±1.1	89.78	80.46	82.19	82.04	1.953	1.905	1.914	1.914
60	13.38 ± 0.01	31.32±1.1	28.82±1.1	34.05±1.6	86.62	68.68	71.18	65.95	1.937	1.836	1.852	1.819
90	18.94 ± 0.01	45.00±1.8	41.86±1.13	50.61±1.8	81.06	55.00	58.14	49.39	1.908	1.740	1.764	1.693
120	22.19 ± 0.02	60.12±2.4	55.54±2.07	62.24±2.3	77.81	39.88	44.46	37.76	1.891	1.600	1.647	1.577

OE:PM1 Orlistat – PEG 4000 Physical Mixture(1:1)
OE:PM2 Orlistat – PEG 4000 Physical Mixture(1:2)
OE:PM3 Orlistat – PEG 4000 Physical Mixture(1:3)

Fig 16 : *In vitro* Release Plots of Orlistat Pure Drug and its Physical Mixture prepared with Eudragit L 100

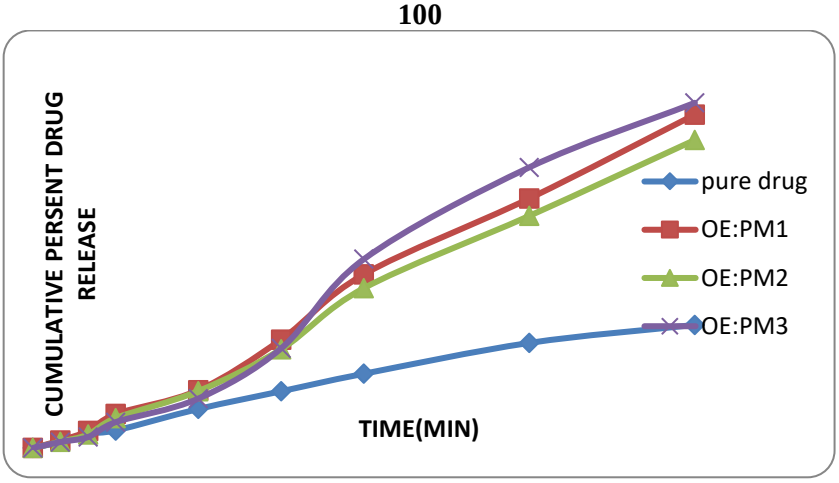


Table 14 : *In vitro* Drug Release Data of Orlistat from various HPMC Solid Dispersions

Time (min)	Cumulative Percent Drug Released (±SD)				Percentage Drug Remaining				Log Percent Drug Remaining			
	Pure drug	OH-SD1	OH-SD2	OH-SD3	Pure drug	OH-SD1	OH-SD2	OH-SD3	Pure drug	OH-SD1	OH-SD2	OH-SD3
0	0	0	0	0	0	0	0	0	0	0	0	0
5	1.09 ± 0.03	1.89±0.05	2.83±0.45	2.94±0.4	98.91	98.11	97.17	97.06	1.995	1.991	1.987	1.987
10	2.57 ± 0.01	6.45±0.06	7.87±0.1	7.99±0.1	97.43	93.55	92.13	92.01	1.988	1.971	1.964	1.963
15	3.15 ± 0.01	12.75±0.1	14.95±0.8	16.32±0.8	96.85	81.25	85.05	83.68	1.986	1.909	1.929	1.922
30	7.03 ± 0.02	21.72±0.7	24.56±0.9	27.31±1.2	92.97	78.28	75.44	72.69	1.968	1.893	1.877	1.861
45	10.22 ± 0.06	33.54±0.6	36.89±1.04	39.96±1.5	89.78	66.46	65.11	60.04	1.953	1.822	1.813	1.778
60	13.38 ± 0.01	46.32±1.1	49.82±1.09	54.05±1.7	86.62	53.68	50.18	45.95	1.937	1.729	1.700	1.662
90	18.94 ± 0.01	50.30±1.8	55.03±1.13	61.61±1.8	81.06	49.70	44.97	38.39	1.908	1.696	1.652	1.584
120	22.19 ± 0.02	62.40±2.4	68.90±2.07	76.24±2.1	77.81	37.60	31.10	23.76	1.891	1.575	1.492	1.375

OH:SD1 Orlistat – HPMC Solid Dispersion(1:1)
OH:SD2 Orlistat – HPMC Solid Dispersion (1:2)
OH:SD3 Orlistat – HPMC Solid Dispersion (1:3)

Fig 17: *In vitro* Release Plots of Orlistat Pure Drug and its Solid Dispersion prepared with HPMC

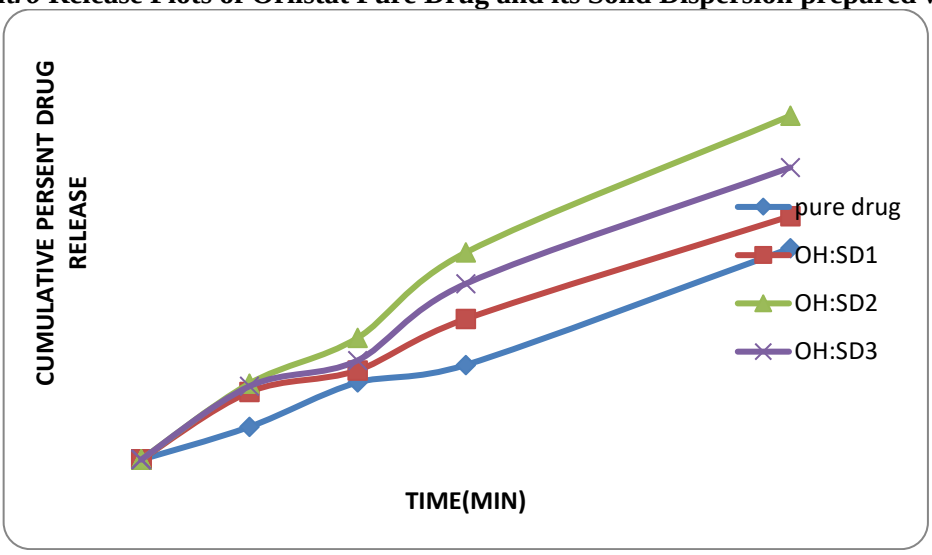


Table 15 : *In vitro* Drug Release Data of Orlistat from various PEG-4000 Solid Dispersions

Time (min)	Cumulative Percent Drug Released (±SD)				Percentage Drug Remaining				Log Percent Drug Remaining			
	Pure drug	OP-SD1	OP-SD2	OP-SD3	Pure drug	OP-SD1	OP-SD2	OP-SD3	Pure drug	OP-SD1	OP-SD2	OP-SD3
0	0	0	0	0	0	0	0	0	0	0	0	0
5	1.09 ± 0.03	2.52±0.05	2.98±0.45	3.42±0.4	98.91	97.48	97.02	96.58	1.995	1.988	1.986	1.984
10	2.57 ± 0.01	7.06±0.06	8.02±0.1	9.40±0.1	97.43	92.94	91.98	90.60	1.988	1.968	1.963	1.957
15	3.15 ± 0.01	13.38±0.1	15.11±0.8	17.32±0.8	96.85	86.62	84.89	82.68	1.986	1.937	1.928	1.917
30	7.03 ± 0.02	21.57±0.7	23.76±0.9	26.73±1.6	92.97	78.43	76.24	73.27	1.968	1.894	1.882	1.864
45	10.22 ± 0.06	34.01±0.6	36.52±1.04	40.27±1.9	89.78	65.99	63.48	59.73	1.953	1.819	1.802	1.776
60	13.38 ± 0.01	48.65±1.1	51.79±1.09	56.05±1.7	86.62	51.35	48.21	43.95	1.937	1.710	1.683	1.642
90	18.94 ± 0.01	67.55±1.8	73.84±1.13	80.67±1.9	81.06	32.45	26.16	19.33	1.908	1.511	1.417	1.286
120	22.19 ± 0.02	69.01±2.4	81.90±2.07	87.20±2.6	77.81	30.99	18.10	12.80	1.891	1.491	1.257	1.10

OP:SD1 Orlistat – PEG 4000 Solid Dispersion(1:1)
OP:SD2 Orlistat – PEG 4000 Solid Dispersion (1:2)
OP:SD3 Orlistat – PEG 4000 Solid Dispersion (1:3)

Fig 18: *In vitro* Release Plots of Orlistat Pure Drug and its Solid Dispersion prepared with PEG 4000

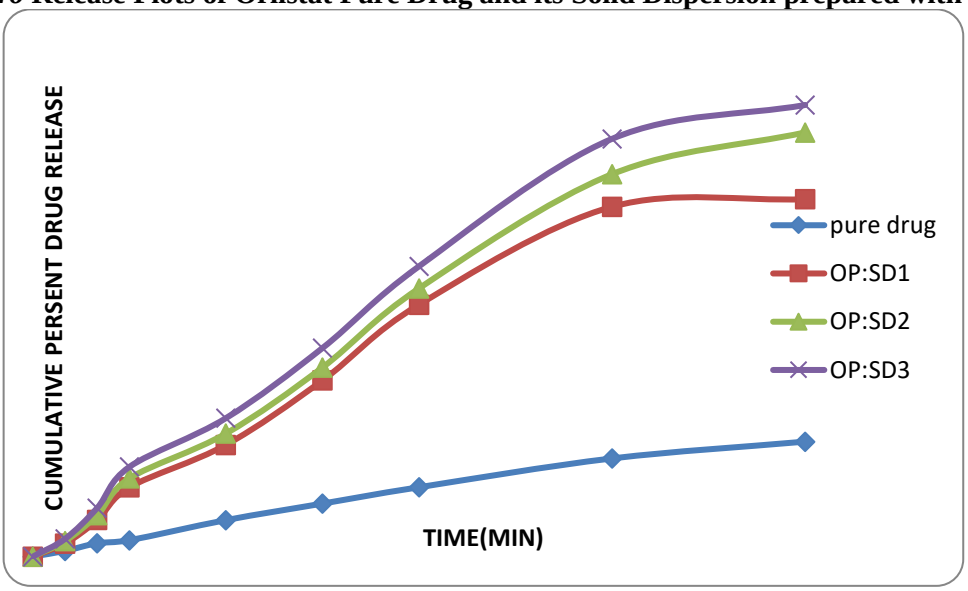


Table 16: *In vitro* Drug Release Data of Orlistat from various Eudragit L 100 Solid Dispersions

Time (min)	Cumulative Percent Drug Released (±SD)				Percentage Drug Remaining				Log Percent Drug Remaining			
	Pure drug	OE-SD1	OE-SD2	OE-SD3	Pure drug	OE-SD1	OE-SD2	OE-SD3	Pure drug	OE-SD1	OE-SD2	OE-SD3
0	0	0	0	0	0	0	0	0	0	0	0	0
5	1.09 ± 0.03	2.53±0.04	2.02±0.45	2.42±0.4	98.91	97.47	97.98	97.58	1.995	1.988	1.991	1.989
10	2.57 ± 0.01	4.06±0.06	3.94±0.1	4.40±0.1	97.43	95.94	96.06	95.60	1.988	1.982	1.982	1.980
15	3.15 ± 0.01	7.70±0.1	7.11±0.8	7.32±0.8	96.85	92.30	92.89	92.68	1.986	1.965	1.967	1.966
30	7.03 ± 0.02	14.57±0.7	12.36±0.9	15.73±1.1	92.97	85.43	87.64	84.27	1.968	1.931	1.942	1.925
45	10.22 ± 0.06	23.01±0.6	19.52±1.04	20.27±1.3	89.78	76.99	80.48	79.73	1.953	1.886	1.905	1.901
60	13.38 ± 0.01	35.23±1.7	29.60±1.09	28.05±1.7	86.62	64.77	70.40	71.95	1.937	1.811	1.847	1.857
90	18.94 ± 0.01	48.15±1.8	43.61±1.13	41.37±1.9	81.06	51.85	56.39	58.63	1.908	1.714	1.751	1.768
120	22.19 ± 0.02	65.61±2.4	58.25±2.07	56.20±2.6	77.81	34.39	41.75	43.80	1.891	1.536	1.620	1.641

OE:SD1 Orlistat – Eudragit L100 Solid Dispersion(1:1)
OE:SD2 Orlistat – Eudragit L100 Solid Dispersion (1:2)
OE:SD3 Orlistat – Eudragit L100 Solid Dispersion (1:3)

Fig 19: *In vitro* Release Plots of Orlistat Pure Drug and its Solid Dispersion prepared with Eudragit L 100

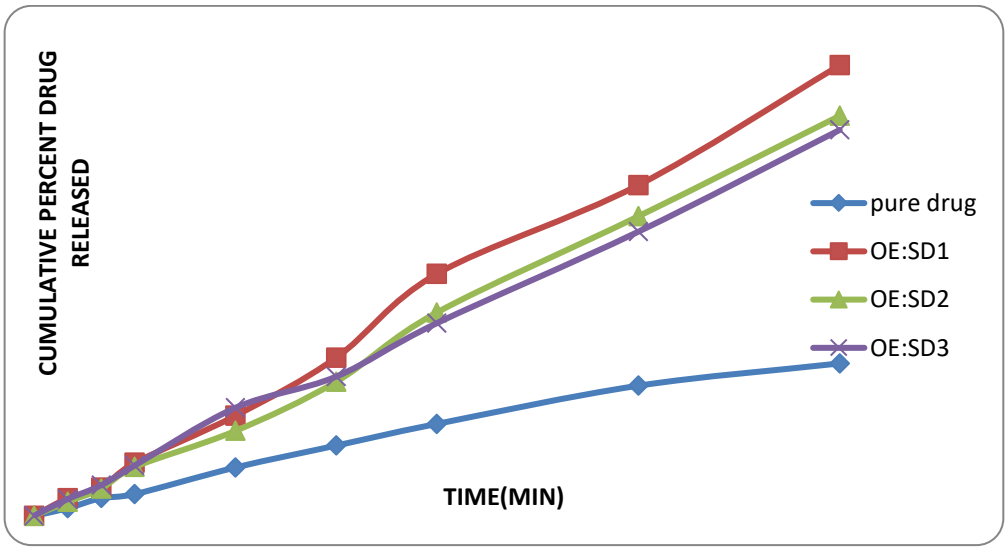


Fig 20: *In vitro* Release Plots of Orlistat Pure Drug and its all Physical Mixture Formulations

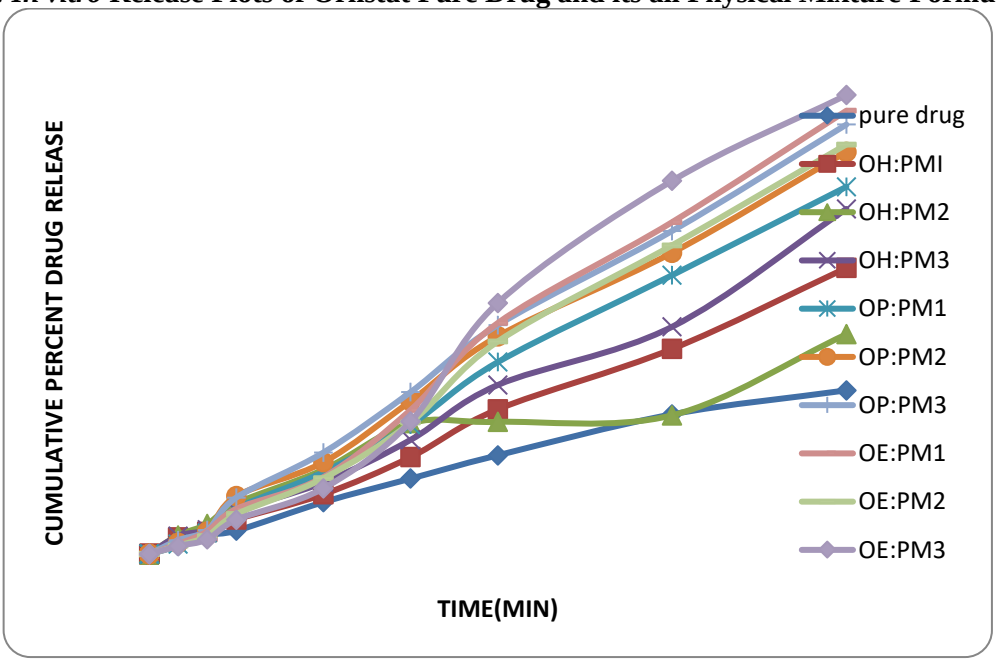


Fig 21: *In vitro* Release Plots of Orlistat Pure Drug and its all Solid Dispersion Formulations

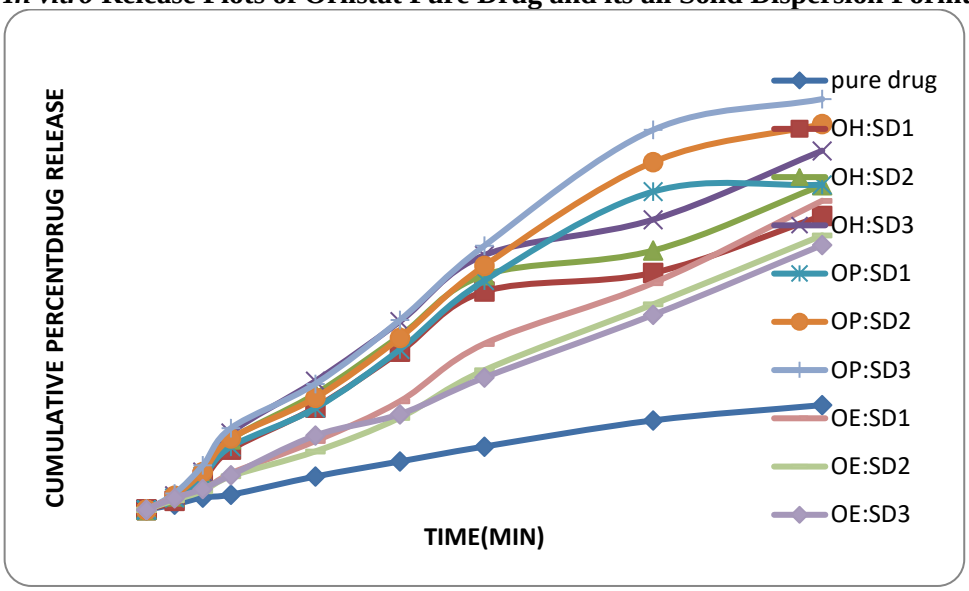


Table 17: Model fitting for formulation OP: SD3

Time(min)	Cumulative % drug release	Log % drug unrelease	Log t	SQRT	Log Cum % release
0	0	0	0	0	0
5	3.42	1.984	0.69897	2.236068	0.534026
10	9.40	1.957	1	3.162278	0.973128
15	17.32	1.917	1.176091	3.872983	1.238548
30	26.73	1.864	1.477121	5.477226	1.426999
45	40.27	1.776	1.653213	6.708204	1.604982
60	56.05	1.642	1.778151	7.745967	1.748576
90	80.67	1.286	1.954243	9.486833	1.906712
120	87.20	1.10	2.079181	10.94445	1.940516

Table 18: Release kinetics of formulation OP:SD3

Formulation	Zero order R^2 value	First order R^2 value	Higuchi R^2 value	Korsmeyer peppas 'n'value
OP:SD3	0.9745	0.9783	0.9483	0.9793

Fig 22: ZERO ORDER MODEL FITTING

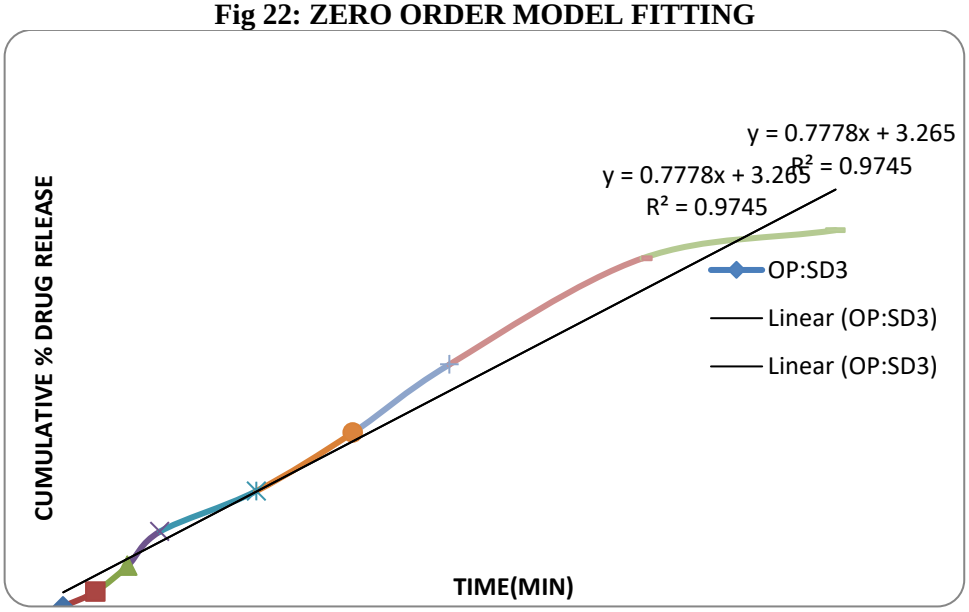


Fig 23: FIRST ORDER MODEL FITTING

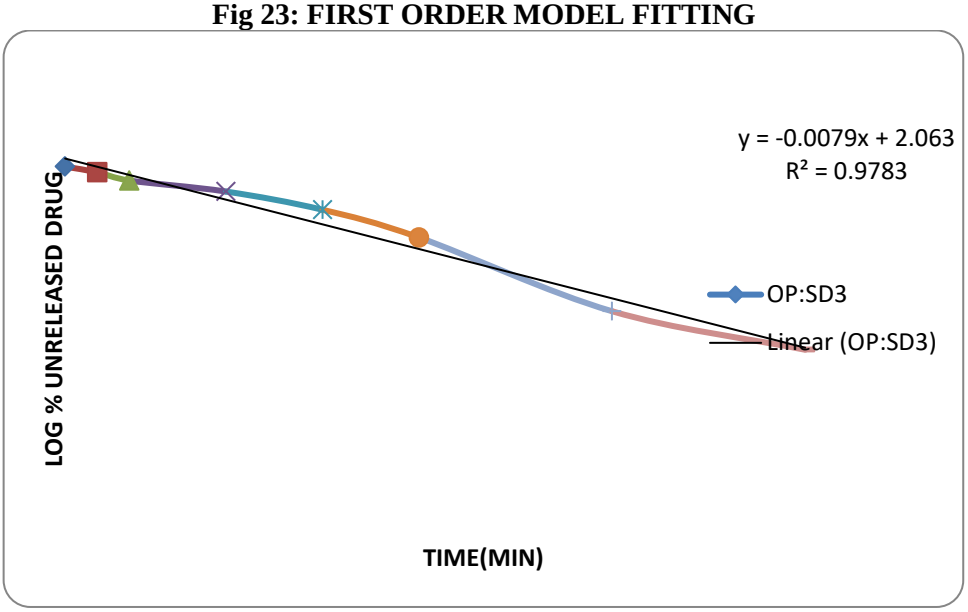


Fig 24: HIGUCHI MODEL FITTING

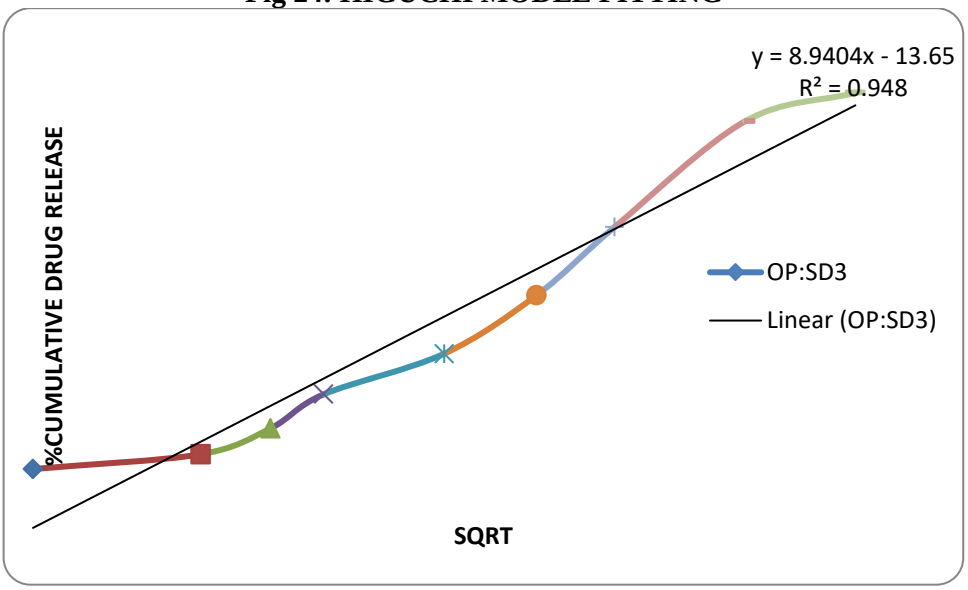
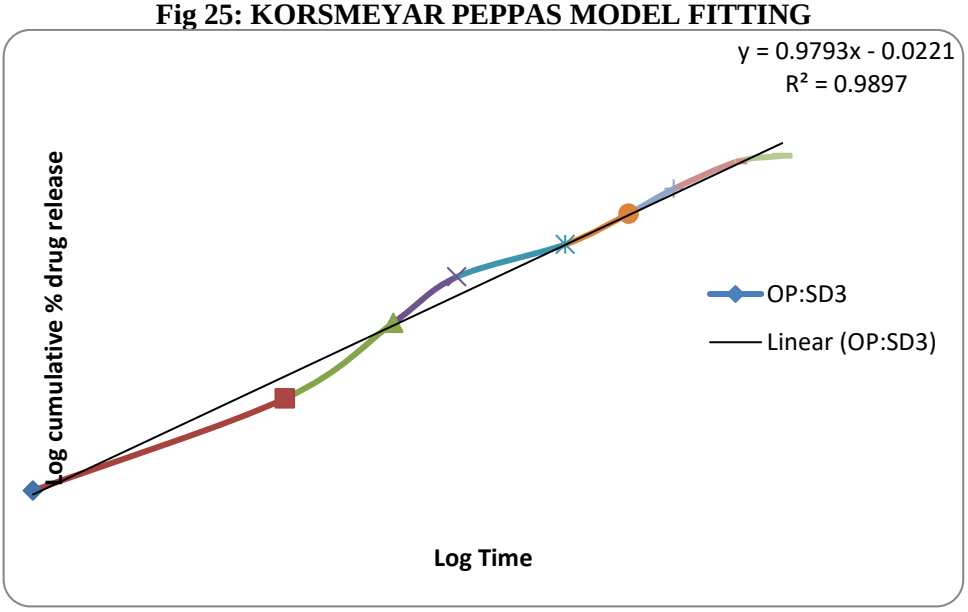


Fig 25: KORSMEYAR PEPPAS MODEL FITTING



DISCUSSION

In the present research work, Orlistat solid dispersions were prepared using hydrophillic polymers such as polyethylene glycol-4000, Hydroxypropyl methyl cellulose and Eudragit l 100 pyrrolidone in the ratio of 1:1, 1:2 and 1:3 by solvent evaporation technique. The prepared formulations were evaluated for number of parameters like solubility, drug content uniformity, drug-polymer interactions, , X-ray diffraction, , *in vitro* drug release studies The results of the above said parameters were shown in various sections of the previous chapter i.e., chapter-5 and the detailed discussion of the evaluation is described in detail in the following sections of this chapter.

Drug-Polymer Interactions:

The drug orlistst has showed characteristic absorption peaks in its IR spectrum at 1770 and 1192. These are due to the characteristic absorption of open chain ketone present in the molecule. Number of peaks has been observed in the absorption range of C–H, this confirms the compound orlistat.The above drug is taken for formulation using HPMC in solid phase. The physical change in drug is not observed. To confirm this the IR spectrum of the formulation is recorded, which showed undisturbed absorption peaks due to C=O of the drug at 1770 and 1192. The peak due to the O–H of the polymer is observed at 3395 indicating the drug has not reacted with the polymer or no evidence of hydrogen bonding could be established.Following the above method, the formulation is prepared using polyethylene glycol-4000 in the solid phase. The formulation so obtained has also identical IR spectrum as that of above, indicating the reaction has not taken place.Similarly formulation has been done Eudragit L 100 in the IR of this formulation (OE:SD1), peak due to the hydroxyl of the polymer is appeared at 3421 cm–1 and peaks due to the drug are observed at 1770 and 1192 supporting the formulation has been done without reaction between drug and polymer.

Solubility:

The solubility studies of orlistat and their solid dispersion systems are studied in distilled water. The results were shown in Table 9 **.**The solubility of orlistat in distilled water is about 3.3µg/ml. whereas solubility of Orlistat in physical mixture prepared with HPMC 5.93, 6.50, 8.06 3µg/ml; with PEG 4000 8.59, 9.36, 10.37 and with Eudragit L 100 8.23; 8.67; 7.29µg/ml; solubility of Orlistat in solid dispersion prepared with HPMC 7.66, 7.83, 8.47 µg/ml; with PEG 4000 9.67, 10.36, 10.99 µg/ml and with Eudragit L 100 8.88, 9.03, 9.43 µg/ml. Among the various formulations prepared, the formulation OP:SD3 (drug-PEG 4000(1:3)) has higher solubility than the other formulations prepared. The results alsosuggest that the solubility of all the formulations prepared showed higher solubility than the pure drug.

Drug Content Uniformity:

The Orlistat solid dispersions prepared were evaluated for the uniform dispersion of the drug throughout the formulation and the results of the study were shown in table-10. The drug was dispersed in the range of 97.08% to 99.80%. So, the results suggest that the drug was uniformly dispersed throughout the formulations prepared.

X-Ray Diffraction Studies:

The pure drug orlistat and some selected formulations such as OH:SD1, OP:SD1 and OE:SD1 were subjected to X-ray diffraction studies and they were shown in figures- 9 to 12 respectively. The X-ray diffractogram of pure drug orlistat shows totally 46 number of intense and sharp peaks, whereas the other diffractograms like formulation OH:SD1, OP:SD1 and OE:SD1shows 36, 32 and 22 number of peaks respectively. The results showed that the number of peaks were reduced and also the intensity of the peaks was also decreased in the formulation diffractograms. The results suggests that the crystalline nature of the drug was converted to amorphous form, which is the reason for the higher solubility, faster dissolution rate and improved bioavailability of drug when it is formulating in the form of solid dispersions.

In Vitro Drug Release Studies:

The orlistat pure drug and its various formulations prepared were subjected to *in vitro* drug release studies and the release data were shown in the table(12to16) and the data was plotted for cumulative percent release versus time (release plots). The orlistat pure drug and its formulation with HPMC Physical Mixture (OH:PM1, OH:PM2, OH:PM3)shows 22.19%, 38.80, 29.80%, 46.8 of drug release respectively at the end of two hours. Similarly the orlistat formulations with polyethylene glycol-4000 (OP:PM1, OP:PM2, OP:PM3) shows 22.19%, 49.80% , 54.54% and 58.24% of drug release respectively at the end of two hours. Similarly Orlistat formulations with Eudragit L 100(OE:PM1, OE:PM2, OE:PM3) releases 22.19%, 60.12%, 55.54%, 62.24% respectively. The orlistat pure drug and its formulation with HPMC Solid Dispersion (OH:SD1, OH:SD2, OH:SD3)shows 22.19%, 62.40%, 68.90%, 76.24% of drug release

respectively at the end of two hours. Similarly the orlistat formulations with polyethylene glycol-4000 (OP:SD1, OP:SD2, OP:SD3) shows 22.19%, 69.01% , 81.90% and 87.20% of drug release respectively at the end of two hours.Orlistat formulations with Eudragit L 100(OE:SD1, OE:SD2, OE:SD3) releases 22.19%, 65.61%, 58.25%, 56.20% respectively. Among the all formulations OP:SD3 (ORLISTAT : PEG 4000) 1:3 ratio shows better cumulative drug release. The overall the rank order of improvement in dissolution properties of oristat with different polymers in all ratios was PEG 4000 > > HPMC > Eudragit L100 > PMs > orlistat.The data obtained for *in-vitro* release were fitted into equations for the zero order and first order, Higuchi, Korsmeyer, and Hixson release models; the interpretation of the data was based on the values(Table 17,18) of the resulting regression co-efficient. In the case of best formulation, the first order and Korsmeyer peppas plots were found to be fairly linear and the 'r' coefficient value for pure drug orlistat and its formulations with polyethylene glycol-4000 (1:3). So the regression data of first order and Korsmeyer peppas plots indicates that the drug was released by first order kinetics and non fickian.Finally, solid dispersions of orlistat: PEG (OP-SD3) prepared in ratio 1:3 showed excellent physicochemical characteristics and was found to be described by the first order and non fickian kinetics, and was selected as the best formulation in this study. Thus the solid dispersion technique found to be effective in increasing aqueous solubility of orlistat.

CONCLUSION:

The concept of formulating solid dispersions of Orlistat containing hydrophillic polymers like polyethylene glycol-4000, Hydroxypropyl methyl cellulose and Eudrgit L 100 offers a suitable and practical approach in serving desired objective of higher solubility, faster dissolution rate and improved bioavailability of drug.

- The present research work carried out on orlistat solid dispersion system using different polymer, we can draw some conclusions from the research work are as follows:
- The solubility study results reveals that the solubility of orlistat from the solid dispersion systems were method dependent and given in the order PEG4000> >HPMC> Eudragit L 100 >PM.
- The results of drug content uniformity study show the uniform dispersion of Orlistat throughout the formulations prepared.
- The results of FTIR shows it may be inferred that there was no interaction between drug and polymers.
- The pure drug orlistat and its solid dispersions were subjected to X-ray diffraction analysis. X-ray Diffractogram study showed the reduced number of peaks and decrease intensity of the peaks in the formulations, this suggests that the crystalline nature of the drug was converted to amorphous form, which is the reason for the higher solubility, faster dissolution rate and improved bioavailability of the drug when it is formulating in the form of solid dispersions.
- The *in vitro* release study was carried out on plain pure drug orlistat and various solid dispersion formulations by employing pH 1.2 acetic buffer as a dissolution medium. This shows an increased release of the drug from the dispersions in comparison to pure orlistat drug.
- *In vitro* data of best drug release formulation was subjected to first order plots, the graphs plotted were fairly linear and the 'r' values of all the formulations were very close to one, indicating the release mechanism followed first order and non fickian kinetics.
- Finally, solid dispersions of orlistat: PEG (OP-SD3) prepared in ratio 1:3 showed excellent physicochemical characteristics and best drug release compared to other formulations. Thus the solid dispersion technique found to be effective in increasing aqueous solubility of orlistat.

BIBLIOGRAPHY

1. Martin A, Swarbrick J, Cammarata A. Physical pharmacy, Philadelphia: Lea&Febiger 1993; 273.
2. Horter D, Dressman JB. Influence of physicochemical properties on dissolution of drug in the gastrointestinal tract. Adv Drug Del Rev 1997; 53:3-14.
3. Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc 1897; 19:930-934.
4. Wagner JG. Fundamentals of clinical pharmacokinetics. Drug Intell Clin Pharma 1931; 5:115-120.
5. Encyclopedia of Pharmaceutical Technology, 2nd Edition, Edited by: James Swarbrick, James MC. Boylan, Published by: Marcel Dekker Inc., New York, Basel, Vol. 1, 2002; Page No. 658, 642-648.
6. Theory & Practice of Industrial Pharmacy. 3rd Edition, Edited by Leon Lachman, Herbert A Liberman, Joseph L Kanig. Published by: Varghese Publishing House, Bombay 1987; Page: 221, 460.
7. Neelam Seedher and Jaspreet Kaur. Solubilization of nimesulide: Use of Co-

solvents. Indian Journal of Pharmaceutical Sciences, 2003 Jan- Feb.; Page No. 58-61.
8. Patrick J Crowley, Luigi G Martin. Physicochemical approaches to enhancing oral absorption. Pharmaceutical Technology Europe, Sept. 1.2004; page 1-8.
9. Encyclopedia of Pharmaceutical Technology. 2nd Edition, Edited by: James Swarbrick, James C. Boylan, Published by: Marcel Dekker Inc., New York Basel, Vol. 2, 2002; Page No. 1677.
10. Biopharmaceutics & Pharmacokinetics. 1st Edition, Edited by: M.K.Jain, Published by Vallabh Prakashan, SU-221, Pitampura, Delhi; Page 29.
11. Rasool AA, Hussain AA, Dittert LW. Solubility enhancement of some water insoluble drugs in the presence of nicotinamide and related compounds. Journal of Pharmaceutical Sciences.1991 April,80(4): 387-393.
12. Biopharmaceutics & Pharmacokinetics – An Introduction. 2nd Edition, Edited by: Robert E Notari, Joyce L, De Young, Raymond C, Anderson, Published by Marcel Dekker Inc. New York 1975; Page 216.
13. Patrick J Crowley, Luigi G Martin. Physicochemical approaches to enhancing oral absorption. Pharmaceutical Technology Europe, Sept. 1, 2004; Page 1-9 (http://www.ptemag.com/ pharmtech europe/ article/ article detail.isp?id=121695).
14. Encyclopedia of Pharmaceutical Technology. 2nd Edition, Edited by: James Swarbrick, James C. Boylan, Published by: Marcel Dekker Inc., New York Basel, Vol. 2, 2002; Page No. 1677-1678.
15. Biopharmaceutics & Pharmacokinetics. 1st Edition, Edited by: M. K. Jain, Published by Vallabh Prakashan, SU-221, Pitampura, Delhi; Page 297.
16. Encyclopedia of Pharmaceutical Technology. 2nd Edition, Edited by: James Swarbrick, James C. Boylan, Published by: Marcel Dekker Inc., New York Basel, Vol. 2, 2002; Page No. 2643.