

A NOVEL FORMULATION OF ORLISTAT SOLID DISPERSIONS USING SOLVENT EVAPORATION TECHNIQUE

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Abstract

Solubility is an important physicochemical factor affecting absorption of drug and there by its therapeutic effect. About 40% of newly discovered drugs are lipophilic and failed to reach market due to their poor water solubility. Solid dispersions proved to have tremendous potential for improving drug solubility. Orlistat is a poor water soluble substance possessing anti-obesity property; in the present study an attempt was made to increase the solubility of orlistat by preparing solid dispersions using solvent evaporation technique. Three different formulations were prepared using Hydroxy propyl methyl cellulose (HPMC), Polyethylene glycol (PEG) and Eudragit with varying ratios of drug and carrier viz. 1:1, 1:2, 1:3 and the corresponding physical mixtures were also prepared. These solid dispersions were evaluated for flowability, solubility characteristics and in-vitro drug release. The in-vitro release of the formulation OP-SD3 was found to be best among all the 9 formulations with a release of 87.2% at the end of 2 hours. Release was best fitted with Korsmeyer-peppas kinetics and it shows that the drug release may follow diffusion mechanism. In-vitro dissolution studies showed that the dispersion system containing orlistat, dissolution of orlistat was retarded which attributed to ionic interaction and gel forming respectively but the solid dispersion containing PEG as carrier gave faster dissolution rate than physical mixture. Thus the solid dispersion technique found to be effective in increasing aqueous solubility of orlistat.

Keywords: orlistat; solid dispersions; solvent evaporation technique

1. Introduction

Orlistat is also known as tetrahydrolipstatin, is a drug designed to treat obesity.¹ Its primary function is preventing the absorption of fats from the human diet, thereby reducing caloric intake. It is intended for use in conjunction with a physician-supervised reduced-calorie diet. Orlistat is the saturated derivative of lipstatin, a potent natural inhibitor of pancreatic lipases isolated from the bacterium *Streptomyces toxytricini*.² However, due to simplicity and stability, orlistat rather than lipstatin was developed into an anti-obesity drug.³ It works by inhibiting gastric and pancreatic lipases, the enzymes that break down triglycerides in the intestine. When lipase activity is blocked, triglycerides from the diet are not hydrolyzed into

absorbable free fatty acids, and are excreted undigested instead. Only trace amounts of orlistat are absorbed systemically; the primary effect is local lipase inhibition within the GI tract after an oral dose. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. Many technological methods of enhancing dissolution characteristics of slightly soluble drugs have been reported in literature such as micronisation, formation of solvates, absorbates, complexes, microspheres and more often solid dispersion. Thus the present study aimed to investigate solubility enhancement of orlistat using various polymers by using solvent evaporation technique.

2. Materials and Methods:

Orlistat is a gift sample obtained from Glukem Pharmaceuticals.pvt.ltd, Hyderabad. HPMC, Polyethylene Glycol, eudragit were also procured from the same company. Dichloromethane obtained from SD fine chem. Ltd, Mumbai. All chemicals are of analytical grade.

2.1. Method of preparation:

2.1.1. 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.

2.1.2. Preparation of solid dispersions: 9 formulations of solid dispersions containing orlistat with HPMC, PEG 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 and Eudragit L100 as shown in Table 1.

3. Pre-formulation studies:

3.1. Solubility Studies⁴ : Weighed accurately about 10gm of pure drug and dissolved each in 5ml of the solvent system i.e. water, chloroform, toluene, hexane, ethanol, n-butane, methanol, acetone in a well closed air tight containers. Then add the successive amount of the drug in to the containers containing solvent until the solution became saturated solution. Then the containers were placed in a thermostat shaker for 24hrs and then calculate the percentage solubility in each container.

3.2. Melting Point⁵: Push the open end of a capillary tube into the powdered drug. Move the powder to the closed end of the capillary tube by tapping it on the table. Repeat until the powdered drug occupies 1-2 mm of the capillary tube end. Then attach the capillary tube to a thermometer and align the bulb of the thermometer with the closed end of the capillary tube. Make a glycerin bath as before by half filling a 100 ml beaker with glycerin. Place the thermometer/capillary tube assembly in the glycerin bath so that the surface level of the powdered drug is beneath the surface level of the water bath. Place the beaker on the burner stand and, stirring frequently to insure even heating, carefully heat the glycerin bath with heat source. Note the temperature at which the powder melts. Remove heat source. Let the powder cool and recrystallize. Repeat the procedure two more times and average the results.

3.3. Flow properties⁶: 500mg of powder drug was weighed accurately and subjected to flow tests such as bulk density, true density, angle of repose etc. Repeated the procedure three times and average the results.

3.3.1. Bulk Density⁶: 500mg of powder drug was weighed accurately and was transferred to a measuring cylinder and its bulk volume was measured out. The same procedure was repeated as triplicate and the average bulk density was calculated out. The bulk density was calculated by using the formula.

$$\text{Bulk Density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}}$$

3.3.2. Tapped Density⁶: 500mg of powder drug was weighed accurately and was transferred to a measuring cylinder and was tapped manually till a constant volume was obtained. The same procedure was repeated as triplicate and the average tapped density was calculated out. The tapped density was calculated by using the formula.

Tapped Density= Mass of the powder/Tapped volume

3.3.3. Angle of Repose ⁶: 500mg of powder drug was allowed to fall through a funnel from certain height of 2m, to form a conical heap of powder on a horizontal surface. The particle will slip and roll over each other when the heap is formed. The slanting side of the heap forms an angle with the horizontal surface which is known as Angle of repose. Angle of repose was calculated by using the formula

$$\tan \theta = h/r$$

Whereas h=height of the heap

r=radius of the base of the heap

4. Evaluation:

4.1. Preparation of standard calibration

graph: Weigh 100mg of the drug and dissolved in the 100ml of suitable solvent and from that pipette out 1ml and dilute to 100ml to get 10µg/ml solution. From this pipette out 1ml and dilute to 10ml to get 1µg/ml solution. From this with draw 0.5, 1.0, 1.5, 2.0 & 2.5 ml of the sample and make up to 10ml with water and observe the absorbance by using UV-Visible spectrophotometer at a wavelength of 254nm.

4.2. Particle Size ⁷: For the determination of the particle size of the powder drug first calibrate the electronic microscope by adjusting the stage micrometer as well as eye piece micrometer then calculate the calibration factor. Then placed the powder drug on the slide and measured the mean diameter of 50 particles. Then calculate the particle size by multiplying calibration factor with mean diameter.

4.3. Excipient Compatibility ⁴: Weighed accurately about 100mg each of powder drug, HPMC, PEG and Eudragit L100. Then admix drug and HPMC (1:1), drug and PEG (1:1) and drug and Eudragit L100 (1:1) in air tight screw cap amber colored vials. Individual drug, polymers also placed in air tight screw cap amber colored vials separately, then kept the vials at room temperature as well as in hot air oven at 40°C for one week and carry out FT-IR analysis with saturated potassium bromide using pellet making method.

4.4. In- Vitro Drug Release ⁸: 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 37°C ± 0.5°C and stirred at a speed of 75 rpm. At different time intervals a 10ml 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 λ_{max} 254nm using UV-Visible spectrophotometer against the medium buffer as a blank. The data obtained from In- Vitro drug release were fitted with various kinetic equations like Zero order, First order, Higuchi, Korsmeyer-peppas, Hixson equation.

4.5. Fourier Transform Infrared Analysis (FT-IR) ⁹: Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, carrier and solid dispersions were obtained using a Perkin- Elmer system 200 FT-IR spectrophotometer using KBr-press under hydraulic pressure of 150kg/cm²; the spectra were scanned over the wave number range of 3600 to 400 cm⁻¹ at the ambient temperature.

5. Results and Discussion:

Table1. Formulation Table

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

Table2. Solubility Studies Data

S.no	Solvent system (ml)	Solubility (gm/ml)
1	Water	0.001
2	Chloroform	0.750
3	Toluene	0.600
4	Hexane	0.550
5	Acetone	0.750
6	Ethanol	1.300
7	n-Butanol	1.250
8	Methanol	1.500
9	PEG 400	0.060
10	PEG 600	0.060
11	Glycerol	0.075
12	Propylene glycol	0.060
13	Sesame oil	0.050
14	Olive oil	0.050
15	Castor oil	0.050

Table3. Derived Properties of pure drug:

Trails	Bulk density (gm / cc)	Tapped density (gm / cc)	Compressibility index (%)	Hauser's ratio	Angle of repose
1	0.2632 ± 0.0002	0.4546 ± 0.0003	0.4214 ± 0.0002	172.75 ± 0.0286	16.4533 ± 0.0249
2	0.2633 ± 0.0002	0.4148 ± 0.0002	0.4148 ± 0.0035	172.56 ± 0.0205	15.7500 ± 0.0216
3	0.2635 ± 0.0002	0.4554 ± 0.0002	0.4216 ± 0.0002	172.94 ± 0.0249	19.6546 ± 0.0285

Table4. Data showing comparative *In-Vitro* % drug release profiles for all the prepared physical mixtures.

	% Drug release of orlistat physical mixtures								
Time (min)	OH-PM1	OH-PM2	OH-PM3	OP-PM1	OP-PM2	OP-PM3	OE-PM1	OE-PM2	OE-PM3
0	0	0	0	0	0	0	0	0	0
5	1.26	1.53	1.44	1.35	1.44	1.53	0.63	0.45	0.09
10	2.79	4.05	3.3	2.88	3.06	3.24	2.97	2.43	1.62
15	4.68	6.89	5.85	6.12	7.11	7.65	6.12	5.4	4.23
30	8.1	11.43	9.72	11.16	12.87	13.77	11.43	10.26	8.91
45	13.14	17.7	15.48	17.55	20.43	21.96	19.26	17.82	15.3
60	19.62	17.8	22.68	26.01	29.52	31.5	31.32	28.8	25.47
90	27.81	18.81	30.96	36.72	40.86	43.92	45.0	41.85	38.07
120	38.8	29.61	46.44	49.7	54.54	58.23	60.12	55.7	78.75

Table5. Data showing comparative *In-Vitro* % drug release profiles for all the prepared formulations.

	% Drug release of orlistat solid dispersions								
Time (min)	OH-SD1	OH-SD2	OH-SD3	OP-SD1	OP-SD2	OP-SD3	OE-SD1	OE-SD2	OE-SD3
0	0	0	0	0	0	0	0	0	0
5	1.89	2.83	24.65	2.52	2.98	3.42	0.46	0.31	0.15
10	6.45	7.87	30.47	7.08	8.02	9.40	3.30	2.83	2.51
15	12.75	14.95	38.34	13.38	15.11	17.28	6.60	5.82	5.34
30	21.72	24.56	49.05	21.57	23.76	26.73	12.11	10.86	10.07
45	33.06	36.53	51.49	34.01	36.52	40.27	20.45	18.57	16.37
60	46.13	49.76	66.10	48.65	51.79	56.02	32.70	29.60	26.60
90	50.30	55.03	72.40	67.55	73.84	80.68	48.17	43.61	39.51
120	62.40	68.90	76.70	69.0	81.0	87.20	65.60	58.25	53.30

Table6. Release kinetics of drug release from Physical mixtures

Release Kinetics	OH-PM1	OH-PM2	OH-PM3	OP-PM1	OP-PM2	OP-PM3	OE-PM1	OE-PM2	OE-PM3
Zero order	0.8217	0.903	0.8169	0.8304	0.8409	0.8415	0.8088	0.805	0.6682
First order	0.9645	0.9393	0.9691	0.9622	0.9613	0.9625	0.9201	0.8927	0.7515
Higuchi	0.8217	0.903	0.8169	0.8304	0.8409	0.8415	0.8088	0.805	0.6682
Korsmeyer-peppas	0.9096	0.928	0.9242	0.91	0.914	0.9192	0.809	0.744	0.4619
Hixson	0.265	0.265	0.265	0.265	0.265	0.265	0.265	0.265	0.265

Table7. Release kinetics of drug release from Solid dispersions

Release Kinetics	OH-SD1	OH-SD2	OH-SD3	OP-SD1	OP-SD2	OP-SD3	OE-SD1	OE-SD2	OE-SD3
Zero order	0.9071	0.914	0.9665	0.8825	0.8786	0.8842	0.8021	0.8053	0.8017
First order	0.9417	0.9417	0.766	0.9532	0.9539	0.9478	0.8972	0.8621	0.791
Higuchi	0.9071	0.914	0.9665	0.8825	0.8786	0.8842	0.8021	0.8053	0.8017
Korsmeyer-peppas	0.9312	0.9436	0.8076	0.9433	0.9442	0.9421	0.7618	0.6875	0.558
Hixson corwell	0.265	0.265	0.265	0.265	0.265	0.265	0.265	0.265	0.265

Fig.1 Standard Graph of Orlistat

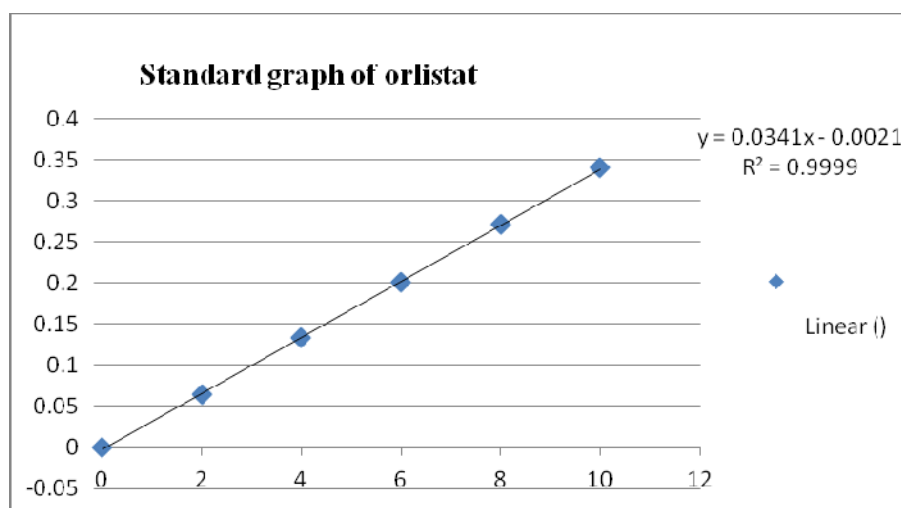
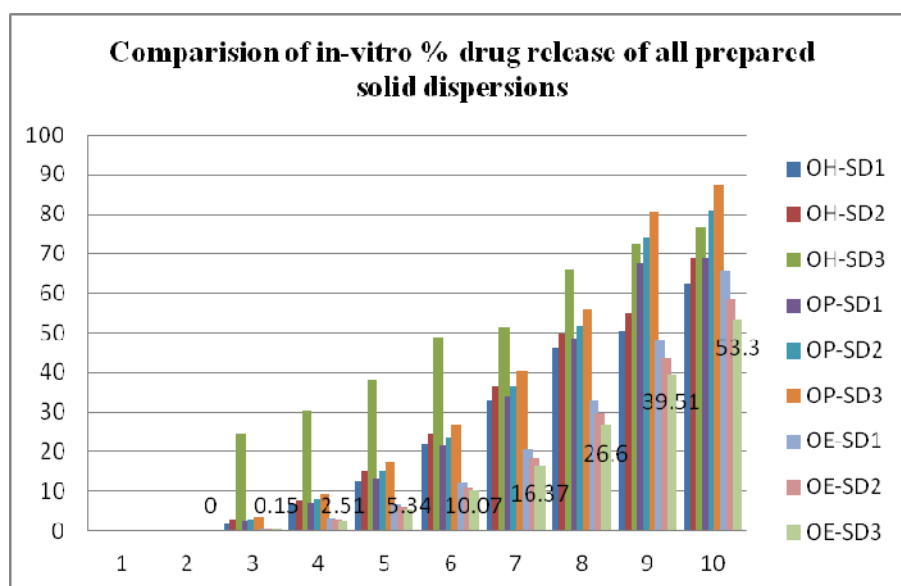
Fig.2 Comparative *In-vitro* % drug release profiles for all the prepared solid dispersions.

Fig.3 Comparative release kinetics of all the prepared solid dispersions

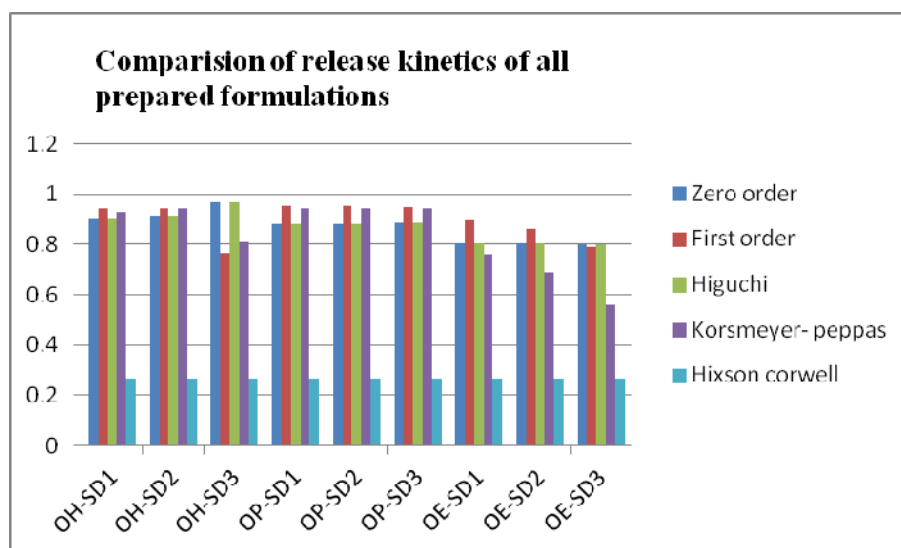


Fig .4 FT–IR spectra of pure drug orlistat

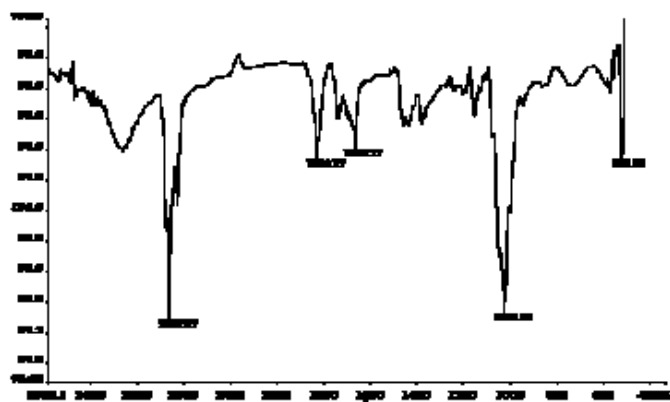


Fig .5 FT–IR spectra of orlistat Solid dispersion (HPMC)

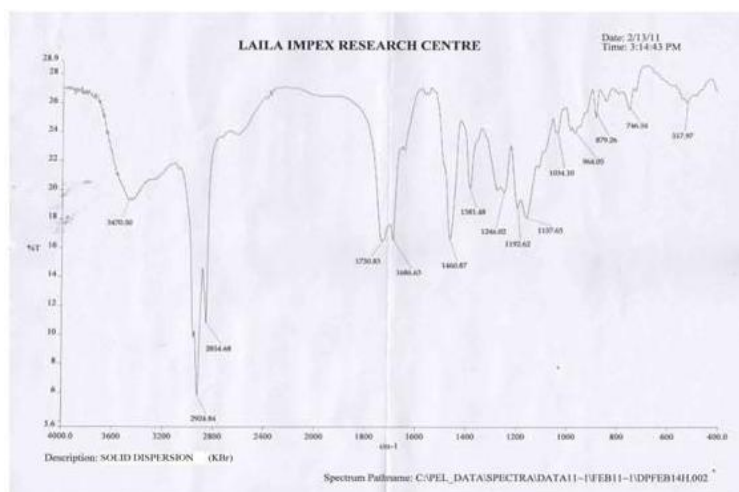
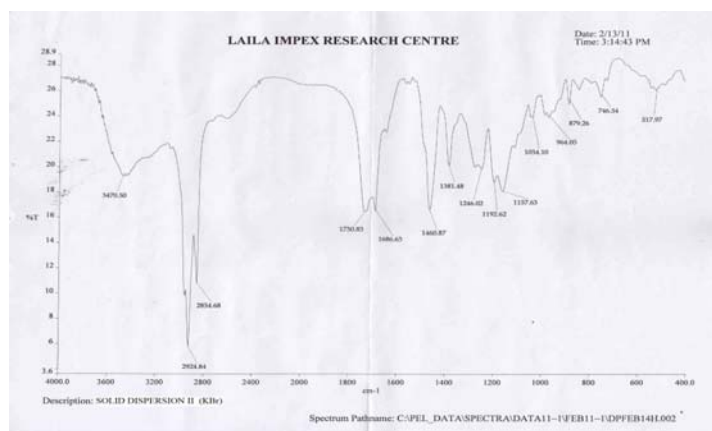
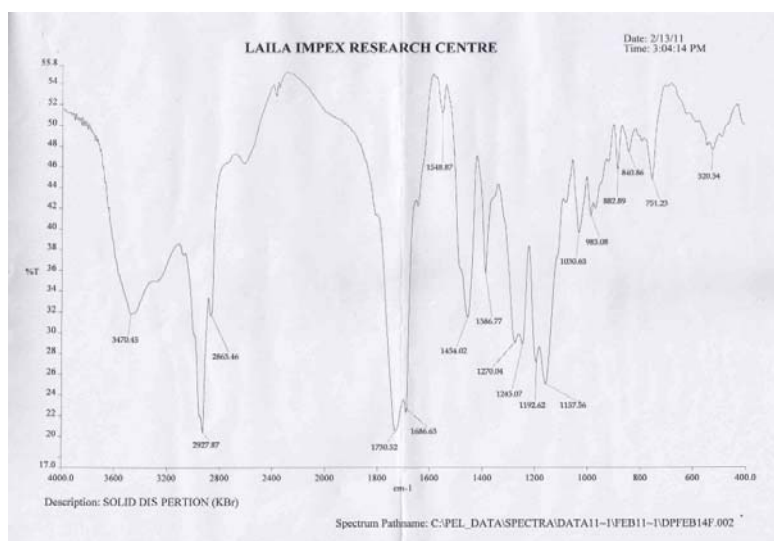


Fig .6 FT–IR spectra of Solid dispersion (PEG)**Fig .7 FT–IR spectra of Solid dispersion (EUDRAGIT)**

The percentage Solubility of the drug in different solvents after 24hrs was tabulated in Table no2. Results 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 as shown in Table 3. FT-IR spectra was taken for solid dispersion containing HPMC, PEG and eudragit as shown in figure 5, 6, 7 and compared with pure drug

FTIR data as shown in fig.4 which reveals 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, Korsmeyer, and Hixson release models; the interpretation of the data was based on the value of the resulting regression co-efficient. The *in-vitro* drug release showed the highest regression value for the Korsmeyer-peppas as tabulated in Table 7 indicating diffusion to be the predominant mechanism of drug release.

Conclusion:

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, as a carrier, gave faster dissolution rates than the physical mixture. 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 zero 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.

References:

1. Bodkin J *et al.* The total synthesis of tetrahydrolipstatin: Australian Journal of Chemistry 2003; 56 (8): 795–803.
2. Barbier P *et al.* Synthesis of tetrahydrolipstatin and absolute configuration of tetrahydrolipstatin and lipstatin: Helvetica Chimica Acta 1987; 70 (1): 196–202.
3. Pommier A *et al.* The first total synthesis of (-)-lipstatin: Journal of Organic Chemistry 1995; 60 (22): 7334–7339.
4. Michael E Aulton. Pharmaceutics: The science of dosage form design. 2nd Ed 2002; 23: 65-73.
5. Faculty.coloradomtn.edu/jeschofnig/c/as/clas.../ch 1-1b 10.htm.
6. Richard J.Smith *et al.* Analysis of drug impurities: Blackwell publishing 2007; -1.
7. Leon lachman *et al.* The theory and practice of industrial pharmacy: 3rd Ed 2004; 182-183.
8. Luypaert J Zhang *et al.* Feasibility study for the use of near infrared spectroscopy in the qualitative and quantitative analysis of green tea, Camellia sinensis (L.), Analytica Chimica Acta 2003; 478(2): 303-312
9. Yoshioka T *et al.* Preparation and properties of vesicles (niosomes) of sorbitan monoesters (span 20, 40, 60, 80) and a sorbitan trimester (span 85): Int J Pharma 1994; 105: 1Y6.