Original Article

Influence Of Eudragit RSPO And Polycaprolactone On The Release Rate And In Vitro Evaluation In The Formulation Of Sustained Release Orlistat Matrix Microparticles

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Abstract

The aim of the study is to formulate Eudragit RSPO and polycaprolactone floating microparticles for enhanced gastric retention and sustained drug delivery by using solvent evaporation technique. Orlistat an anti-obese drug, was used to design gastro retentive drug delivery system. The formulated microparticles were observed for percentage recovery, swelling index, in vitro buoyancy studies and percentage drug release. The physio chemical properties of the microparticles were also studied by using drug-polymer compatibility study and found the formulation complies with the standards. In vitro drug release characteristics of the formulated microparticles were studied in simulated gastric fluid of pH 1.2 and simulated intestinal fluid of pH 7.4 respectively and found the formulation F4 containing equal amount of Eudragit RSPO and Polycaprolactone released the drug in a sustained manner in both pH conditions of 1.2 and 7.4. Floating microparticles of Orlistat were successfully prepared and it can be concluded that the formulated floating microparticles of orlistat can be used for sustained action in the stomach to improve the absorption.

Keywords: Orlistat, Eudragit RSPO, Polycaprolactone and Gastro retentive drug delivery system.

Introduction

Floating drug delivery system are better suited for poorly soluble drugs at alkaline pH acting locally and primarily absorbed in the stomach.[1] Such drugs have a narrow window of absorption and have poor solubility in the intestinal and colonic environment. To achieve better floating behaviour in the stomach the density of the delivery system should be less than that of the stomach content.[2]

On health front, people struggle with increasing rate of obesity which is recommended as a leading cause for a number of pathological conditions (Ex: Coronary heart disease, High blood pressure, Metabolic syndrome, Type 2 diabetes etc.).[3,4] In recent research floating granules have been developed for orlistat to deliver the incorporated therapeutic agent in effective concentration and extended time. Floating characteristics and the gastric content of such formulation is able to provide a prolonged retention in gastric region.[5]

Eudragit RSPO is a copolymer of acrylates with quaternary ammonium groups. It is a pH dependent polymer soluble in gastric pH lower than pH 5.0. It has good adhesion, high pigment binding as well as low viscosity. It is also used in transdermal drug delivery system as it produce aggressive transparent film.[6-8]

Polycaprolactone is one of the FDA approved biodegradable polyester synthetic polymers. It is a crystalline polymer with melting point of 60 to 65 °C. It is a hydrophobic polymers used as a biomaterial for human bodies and it also used as a polymer for sustained release dosage form and targeted drug delivery system.[9-11]

Floating microparticles were prepared by solvent evaporation technique and were successfully tested for 12 hours drugs release pattern. The developed formulation of Orlistat were found to be safer and more effective

which is the need of the present situation as an alternate drug delivery system for a highly prevalent chronic disease like obesity.[11-13]

Materials and Methods

Orlistat (Purity 99.8%) standard was procured from Alli capsules (GSK) - Only USFDA Approved drug under "OTC". Eudragit RSPO (Evonik, Germany) (Purity 99%). Polycaprolactone, (Mw ~14,000) (Sigma Aldrich). PVA (Purity 98%) (Merck, Germany). Dichloromethane (DCM) (Merck, Germany). Filter paper (Whatman filter paper no. 40) and double distilled water (DDW) was used throughout the studies collected from laboratory.

Drug solubility studies

Orlistat solubility studies were conducted in various buffers like 0.1 N Hcl , pH 3.0 Glycine buffer, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and pH 7.2 phosphate buffer. [14]

Drug-Excipient compatibility studies:

FTIR:

Drug excipient compatibility study was performed on different excipients of choice in the formulation to determine the compatibility of the excipient with drug at accelerated conditions. The physiochemical compatibility between orlistat, eudragit RSPO, polycaprolactone was carried out by subjecting to Fourier transform infrared spectrophotometer. KBr pellet method was used as a sampling technique. The samples were prepared by mixing 100 mg of orlistat drug with 100mg of different excipients used in the preparation of floating microparticulate system. These samples were scanned under diffuse reflectance mould, and the spectra were recorded in the wave number region between 4000 cm-1 to 400 cm-1. The spectra obtained for the pure drug was compared with that of the physical mixtures of the drug with polymers.[15]

Melting point

DSC:

This technique calculates the heat loss or gain that occurs due to transitions (Physical or chemical or both) as a sample was subject to a pre-determined temperature change. The physical incompatibilities of the drug and different excipients used in the formulation of floating microparticulate system were evaluated quickly by Differential Scanning Calorimetry (DSC) as it differs in the appearance. The DSC thermogram of the pure orlistat and various excipients were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10 °C/min over a temperature range of 50 to 300 °C.[16]

Preparation of microparticles

Orlistat loaded floating microparticles were formulated with solvent evaporation technique using Eudragit RSPO and polycaprolactone which is dissolved in dichloromethane (DCM)at 25°C, individually stirred at 250 rpm in separate beaker positioned on a hot plate with magnetic stirrer. Stirring was continued until clear solution is obtained. Orlistat were separately dissolved in DCM stirred at 300 RPM using magnetic stirrer at 25°C to obtain a clear solution of Orlistat. This solution was added dropwise into the polymeric solution at 300 RPM. Both the solution was stirred to obtain a clear homogenous solution. 1% PVA solution was prepared individually at 80 °C. Homogeneous mixture of drug and polymer were taken in a syringe and added dropwise into 1% PVA solution maintained at 37°C with continuous stirring at 800 RPM using magnetic stirrer. After complete evaporation of DCM the microparticles were filtered using Whatman filter paper and separated and collected. The filtered microparticles was kept in desiccator for complete drying for further use.[17]

Table 1

Feed composition of synthesized Microparticles

S.No	Formulation	Eudragit RSPO/Polycaprolactone ratio	Wt. of. Eudragit RSPO (mg)	Wt. of PCL (mg)	Conc. Of. PVA W/V(%)
1.	F1	1:0	1000	0	1

2.	F2	0.9:0.1	900	100	1
3.	F3	0.7:0.3	700	300	1
4.	F4	0.5:0.5	500	500	1
5.	F5	0.3:0.7	300	700	1
6.	F6	0.1:0.9	100	900	1

Particle Size determination by Malvern analyzer

The orlistat microparticles was diluted with suitable solvent before analysis. The size analysis, both mean particle size and width of distribution (polydispersity index) was done using Zetasizer Nano instrument (Nano ZS90, Malvern Instruments, Malvern, UK). The same dispersion was used for determination of zeta potential.

Particle Size determination by sieve analyzer

Weight accurately 20 gms of orlistat microparticles and loaded in the sieve analyzer. The experiment should be carried out in a condition that do not cause sample to gain or lose moisture. The analyzer is made to run for the time period of five minutes and calculated the weight retained in each sieve and tabulated.

Degree of hydration of microparticles

Dehydration of microparticle is defined as the ratio between the weight of the microparticle to the weight of the dried microparticles. The freshly formulated microparticles were weighed immediately and it is represented as M1. the microparticles were allowed to dry until a constant weight was achieved and they are reweighed again and is represented as M2. The degree of hydration of microparticles can be represented by the following equation[18]

Percentage microsphere hydration = M1/M2*100

Moisture pick up study

Moisture pick up study for Orlistat API was done at different Relative humidity conditions by maintaining temperature at 25°C± 2°C in desiccators by preparing the following saturated solutions

Table 2

Various reagents with its Relative humidity

S.No	Reagents	Relative Humidity (%)
1.	Potassium nitrate	92
2.	Sodium chloride	75
3.	Magnesium nitrate	52
4.	Potassium carbonate	43

Recovery of microparticles

Recovery or percentage yield of the microparticles is defined as the ratio of weight of microparticles recovered or collected to the weight of all solid contents taken initially. Dried microparticles were weighed to determine the recovery of the micropartilces.[22]

Percentage yield = Weight of the microparticles(mg)/ The weight of all solid species taken at beginning (mg)* 100

Floating strength determination

Orlistat loaded floating microparticles were studied for their floating ability in the simulated gastric media containing 0.1N HCL. USP dissolution apparatus type II was used to determine the floating behaviour of the formulations. 500ml of 0.1N HCL was used as a medium which is maintained at 37 ± 0.5 °C and 50RPM.The total floating time and floating lag time was observed, and percentage of floating microparticles can be calculated using the formula.[19]

% of floating microparticles = Weight of floating microsphere after 12 hours/Initial weight of floating microparticles *100

Determination of drug loading

To determine the percentage of drug loaded in different formulation of microparticles, an accurately weighed microparticles were downsized and dissolved in specific amount of solvent(DCM) and it is diluted with 0.1 in HCL contained in a water bath. The solvent was removed by agitating the mixture at 37 °C and the microparticles were kept for 12 hours at 37°C. 0.45m range filter was used to remove the polymers and the final solution was analysed at a wavelength of 294nm using UV visible spectrophotometer. Percentage drug loading was determined by using the formula

%Drug Loading= Mass of drug in microspheres/Mass of microspheres*100

Swelling index

Transfer 1gm of orlistat microparticles to a 25 ml stoppered measuring cylinder. Fill the cylinder up to 20 ml mark with water. Agitate gently occasionally during 24 hour and allowed to stand. Measure the volume occupied by the swollen. The swelling index can be calculated using the formula 20,21

S1= W2-W1/W1*100

In vitro dissolution study

The in vitro drug release rates of orlistat from various microparticles formulations were determined and compared with those of orlistat marketed formulation. A specified dose of orlistat was placed in 500ml of 0.1M hydrochloric acid (pH 1.2) as a dissolution medium and maintained at 37± 0. 5°C. Drug release study was performed using USP dissolution apparatus type II rotated at 100rpm for 12 hrs. Aliquots of 5ml were withdrawn at specified time intervals. The samples were filtered, and the medium was replaced with a equal amount of fresh medium to maintain the sink condition. The amount of orlistat present in the sample were determined using UV spectrophotometry at 229nm. Cumulative percentage of drug release was calculated, and the results were tabulated.[23]

Results and Discussion

Drug solubility:

Table 3

Solubility of orlistat at various buffer

S.No	Medium	Solubility in mg/ml
1.	0.1N Hcl	2.15
2.	pH3.0 Glycine buffer	0.52
3.	pH 4.5 acetate buffer	1.15
4.	pH 6.8 phosphate buffer	2.38
5.	pH 7.2 phosphate buffer	12.69

Orlistat solubility studies were conducted in various buffers mentioned above and the results were discussed in the Table:3. It shows maximum solubility in. pH 7.2 phosphate buffer. Hence there will no discrimination is possible for dissolution in this media. Glycine buffer shows the least solubility, however maximum dose will be soluble in water hence water can be tried for discriminatory dissolution test. Solubility in Glycine buffer, 4.5 acetate buffer, 6.8 phosphate buffer, & water is almost same. I.e. in the range of 0.5- 2.5mg/mL. Orlistat shows the maximum solubility in 0.1N Hcl and pH 7.2 phosphate buffer. Hence it can be used as the dissolution media.

FTIR

Figure 1

IR spectra for the physical mixture

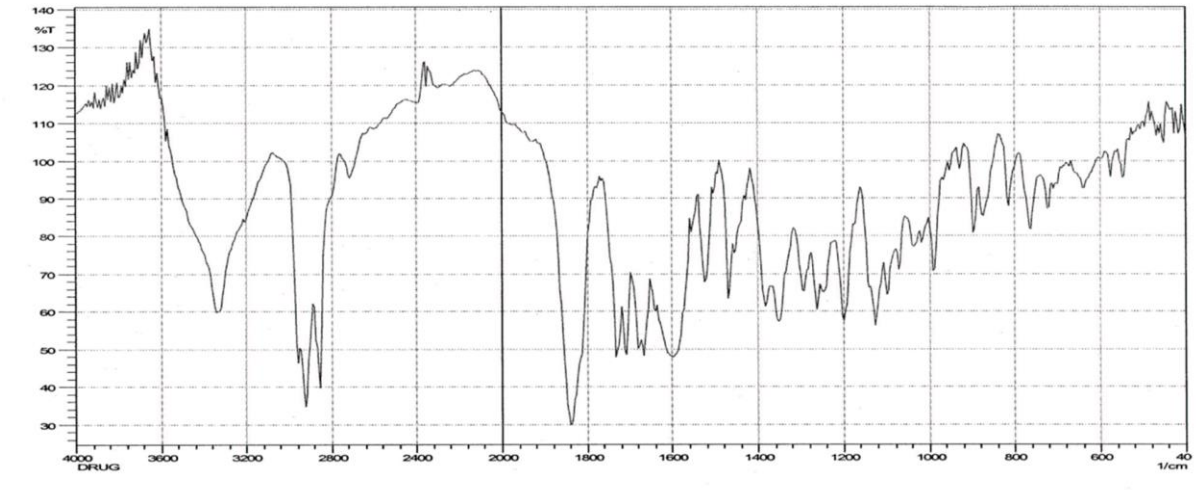


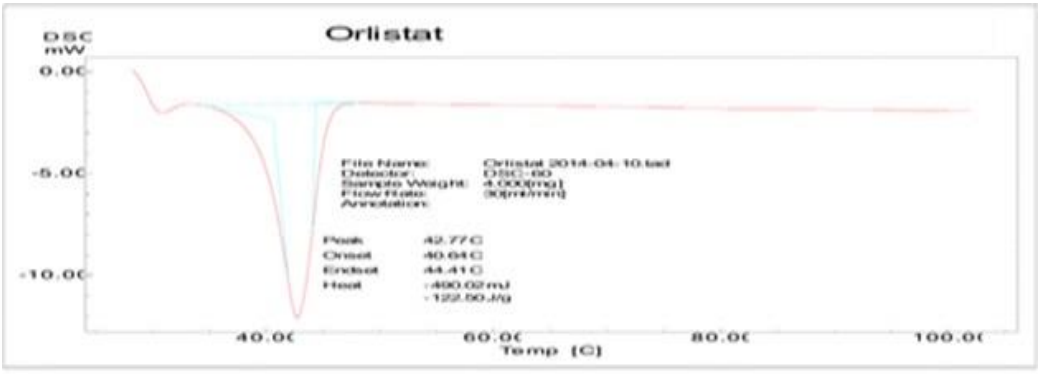
Table 4
IR spectra of orlistat

Functional Groups	Wave number (cm^{-1})
N-H (Stretch)	3327
N-H (Bend)	1567
C-H (Aliphatic)	2920
C=O(Stretch)	1708
C-C(Stretch)	1469
C=C (Stretch)	1523
C-N (Stretch)	1199

Compatibility studies of Orlistat and Eudragit RSPO polymers were conducted by employing IR spectroscopical study. IR Spectra of the physical mixture of drugs and polymer were shown in (Figure:4). The characteristic peaks of Orlistat were observed with the spectra of the physical mixture.[33] It was inferred that the FTIR results indicates that no interaction existed between the drug and polymers as the identical principle peak were observed in all the cases.

DSC of orlistat

Figure 2
Thermogram of Orlistat



Thermograms of pure orlistat and drug polymer complex were represented in (Figure:2) The DSC curve of Orlistat showed an endothermic peak at 42.77°C that is in accordance to the orlistat fusion point. DSC results for the orlistat tablet formulation, with and without orlistat does not show any fusion endothermic peak of the

crystalline form of orlistat. Hence the formulated floating microparticles with orlistat and polymers does not get influenced with the process parameters of the formulation.

Particle size distribution (By Malvern particle counter)

Orlistat was analyzed for powder particle size distribution by means of malvern particle counter by using procedure of particle size determination by malvern particle size analyzer and the results were shown in Table: 5

Table 5

Particle size determined by Malvern particle counter

DRUG API	
Distribution of Particle Size	**Particle Size in microns**
D10	51
D50	95.7
D90	152

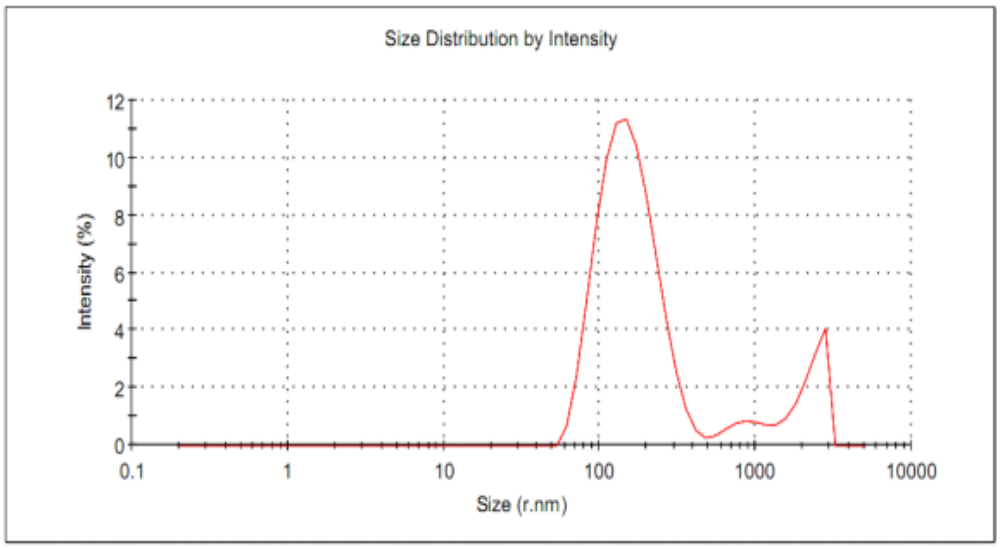
It has been found that around 10% of orlistat having particles in 51 µ size and 50% of the particles is in the range of 95.7µ and 90% of the particles are present in the range of 152µin size. (Figure:4)

It has been found that most of the drug orlistat particles were in the range of 150µ.

PSD of orlistat

Figure 3

Particle size distribution intensity



The particle size distribution graph shows that the majority of the particles lies in the size range of 100-1000µm (Figure:3), which implies the formation of particles in the micron range.

Particle size distribution

The particle size distribution of orlistat was analyzed by means of Mechanical sieve shaker (Retsch). it was performed by using the procedure of sieve analysis of particle size and the results were shown in Table: 6

Table 6

Particle size determined by sieve method

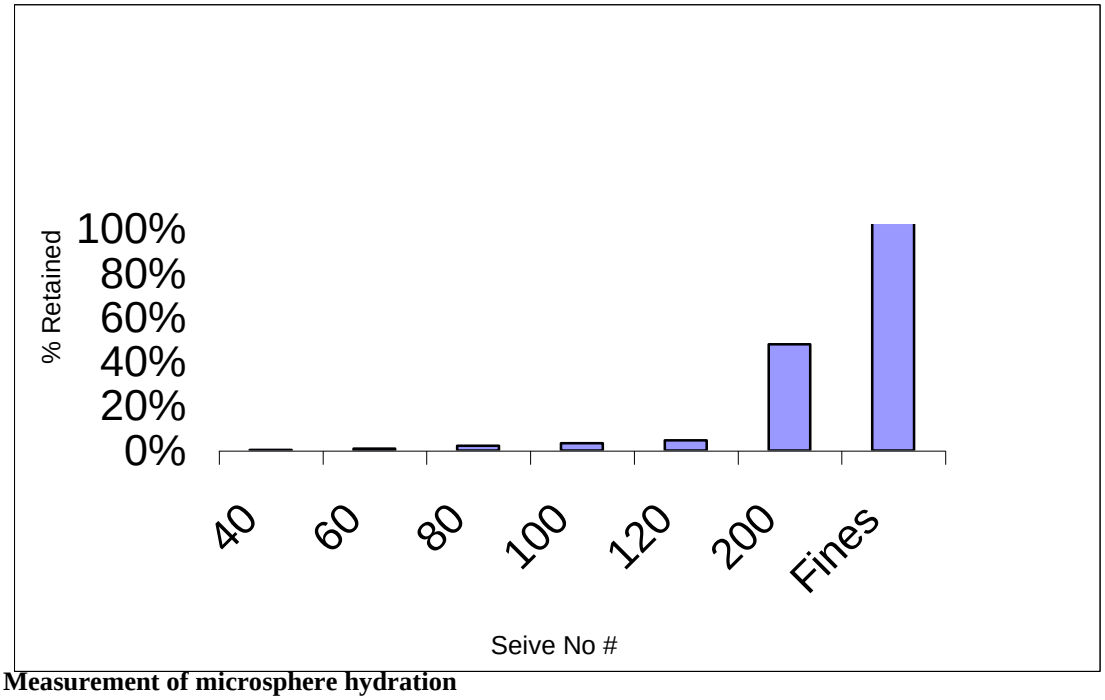
DRUG			
Amplitude: 60		**Time: 5 minutes**	
Weight of the sample taken: 20 gm			
Sieve No.	**Initial Wt.(gm)**	**Final Wt. (gm)**	**% Retained**
20	212.40	212.40	-
30	206.60	206.60	-
40	190.91	190.98	0.35
60	178.01	178.17	0.80
80	177.00	177.43	2.15
100	174.21	174.86	3.25
120	173.63	174.55	4.60
200	169.92	179.52	48.00
Fines	137.00	145.04	40.025
	Total		99.65

It has been informed that around 48% of orlistat retained in 200# mesh which are in 120 µ size. Similarly 40.02%, 4.60%, 3.25 % ,2.15% of orlistat of particle size 75µ, 150µ 180µ and 250µ were retained in 120#, 100#, 80# and 60# meshes respectively. (Figure:5)

It has been found that all the orlistat used for the formulation was in the particle size range of 75µ-250µ.

Figure 4

Bar graph representing particle size distribution



Measurement of microsphere hydration

The amount of hydration depends on the polymer's hydrophilicity. The polymer that swells more in water is called as hydrophilic and at least is called as hydrophobic. Since the polycaprolactone is hydrophobic in nature, the degree of hydration was decreased and can retain only small amount of water in the microparticles. Eudragit RSPO is a polymer that is soluble at pH less than 6 and swells in water. So the degree of hydration got increased when the concentration of Eudragit RSPO was increased. The permeation of water inside the microparticle plays a crucial role with the drug release pattern.

Table 7

Determination of the hydration capacity of the formulated microparticles.

S.No	Formulation	Mean weight of Wet Microparticles (mg)	Mean weight of dry Microparticles (mg)	Microsphere Hydration (%)
1.	F1	1380	806	171.21
2.	F2	1405	865	162.42
3.	F3	1369	897	152.61
4.	F4	1314	900	146.00
5.	F5	1221	885	137.96
6.	F6	1020	775	131.61

Moisture pick up study

The moisture pick up study of orlistat was performed and the results were shown in Table: 8

Table 8

Percentage sorption of orlistat at different relative humidity

RELATIVE HUMIDITY	43%RH	52%RH	75%RH	92%RH
DURATION(h)	% SORPTION (% MOISTURE PICK UP)			
0	0	0	0	0
2	0	0.199	0.414	0.624
4	-0.036	0.149	0.222	0.713
6	0.071	0.232	0.498	0.920
24	-0.042	0.166	0.364	0.934
48	0.049	0.272	0.685	1.120
72	-0.220	0.139	0.584	0.990
96	0.055	0.238	0.594	1.163
120	-0.110	0.113	0.378	0.866
144	-0.139	0.126	0.462	1.006
168	-0.117	0.169	0.560	1.156

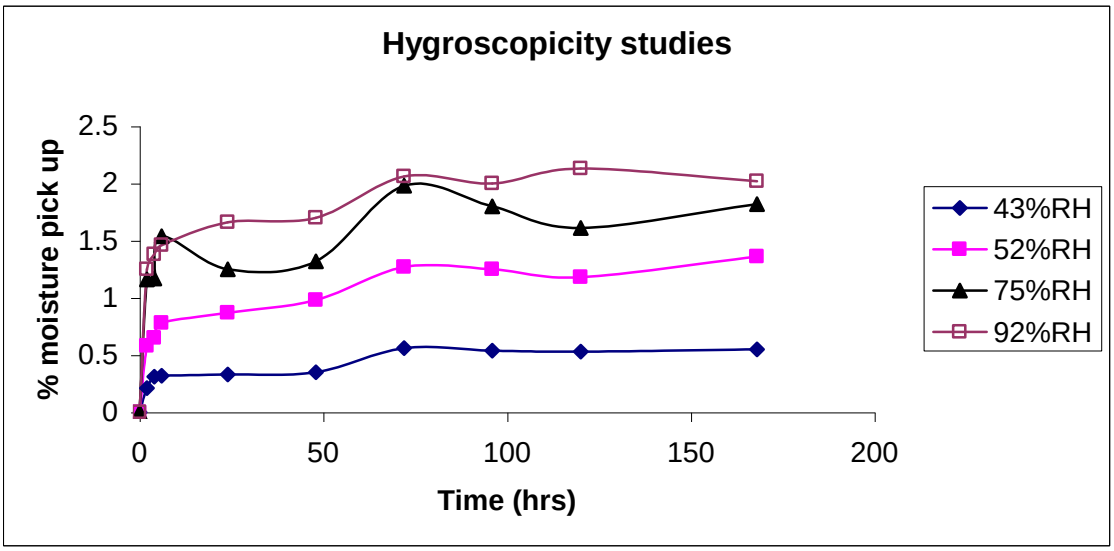
There was no physical change observed in orlistat from all the above condition for 168 hrs. Orlistat showed the positive sorption of moisture with humidity. Equilibrium moisture content achieved is approximately in 72 hours, after this time there was no significant moisture pickup was observed. Hence material is considered as non-hygroscopic.

There is approximately 1-2 % moisture pickup observed at higher humidity hence orlistat should be protected from high humidity.

At 52 % humidity orlistat showed the 0.272 % moisture pick up in 48 hours therefore it should be processed below 52% RH (Preferably 50% RH and 25°C± 2°C)(Table:8).

Figure 6

Graph representing moisture pickup of orlistat at various relative humidity



Recovery percentage of microparticles

Table 9
Recovery percentage of microparticles

S.No	Formulation	Mean Input of all solid contents (mg)	Mean output (mg)	% Recovery of Microparticles
1.	F1	1250	805	64.4
2.	F2	1250	865	69.2
3.	F3	1250	880	70.4
4.	F4	1250	900	72.0
5.	F5	1250	910	72.8
6.	F6	1250	887	68.0

On increasing the concentration of polycaprolactone the recovery of microparticles got increased. As the hydrophobic nature of polycaprolactone, results in decreased chances of aggregation of microparticles. Irregular stirring speed and also the agglomerate formation of polycaprolactone affected the final recovery percentage of microparticles. Less solvent evaporation and irregular shaped microparticles formation were also affected the recovery percentage of microparticles. The Table:9 indicates a percentage recovery of microparticles

In vitro floating ability of microparticles

Buoyancy or floating ability of formulated microparticles was evaluated in simulated gastric fluid (at pH 1.2). it was observed that the formulation F6 maximum floating ability because the concentration of polycaprolactone is high. Polycaprolactone is a hydrophobic polymer and does not dissolve in gastric fluid. Whereas on increasing the concentration of Eudragit RSPO the floating abilities of microparticles got decreased, As Eudragit RSPO is a water soluble polymer in gastric fluid. all the 6 formulation have floating ability between 55 and 85%. The Table 10 indicates the floating ability of formulated microparticles in gastric medium.

Table 10
Percentage floating ability of microparticles

S.No	Formulation	Initial weight of microparticles (mg)	Weight of floating microparticles (mg)	% Floating ability
1.	F1	50	31.2	62.4
2.	F2	50	34.8	69.6

3.	F3	50	36.4	72.8
4.	F4	50	38.8	77.6
5.	F5	50	40.6	81.2
6.	F6	50	42.4	84.2

Drug loading and encapsulation efficiency of microparticles:

The drug loading and encapsulation efficiency of the microparticles were investigated for the effect of varying polymer ratio. The Table 11 and 12 describe the percentage drug loading and encapsulation efficiency of the microparticles. From the table it is clear that the percentage of drug loading got increased on increasing the concentration of eudragit RSPO. It is due to the formation of hollow microparticles having large numbers of pores which helps in loading of drugs. For the formulation F4 containing 50:50 ratio of eudragit RSPO and PCL, The encapsulation efficiency was higher. When the concentration of polycaprolactone was increased beyond 50%, the encapsulation and drug loading capacity got decreased, Which will be due to the hydrophobic nature of polycaprolactone.

Table 11

Percentage drug loading of microparticles

S.No	Formulation	Mass of microparticles (mg)	Mass of drug in microparticles (mg)	% Drug Loading
1.	F1	50	5.253	10.506
2.	F2	50	5.672	11.344
3.	F3	50	5.992	11.984
4.	F4	50	6.492	12.984
5.	F5	50	5.636	11.272
6.	F6	50	4.239	8.478

Table 12

Percentage encapsulation efficiency of microparticles

S.No	Formulation	Theoretical loading (mg)	Actual loading (mg)	Encapsulation efficiency (%)
1.	F1	250	115.27	46.108
2.	F2	250	123.87	49.540
3.	F3	250	147.32	58.928
4.	F4	250	158.68	63.472
5.	F5	250	142.87	57.148
6.	F6	250	132.66	53.064

In vitro dissolution study

Table 13

Percentage cumulative drug release of orlistat at pH 1.2

S.No	Time in Hrs	% Cumulative Drug Release					
		F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	1	23.2	22.4	20.1	19.5	18.2	16.9

3.	2	47.8	43.2	36.2	33.2	25.2	23.5
4.	4	58.9	56.7	52.2	47.5	39.9	37.6
5.	6	69.2	64.1	54.9	51.6	48.8	39.3
6.	8	74.6	70.2	61.7	59.5	55.2	44.8
7.	10	84.8	78.5	69.9	68.8	65	54.9
8.	12	92.1	84.4	76.2	75.8	71.4	65.3

Figure 7

Percentage cumulative drug release of orlistat at pH 1.2

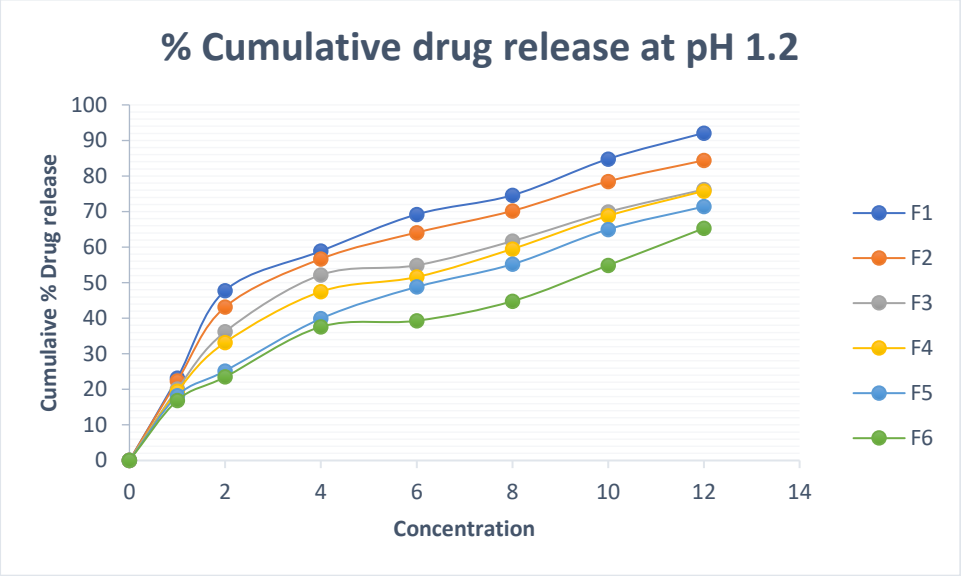


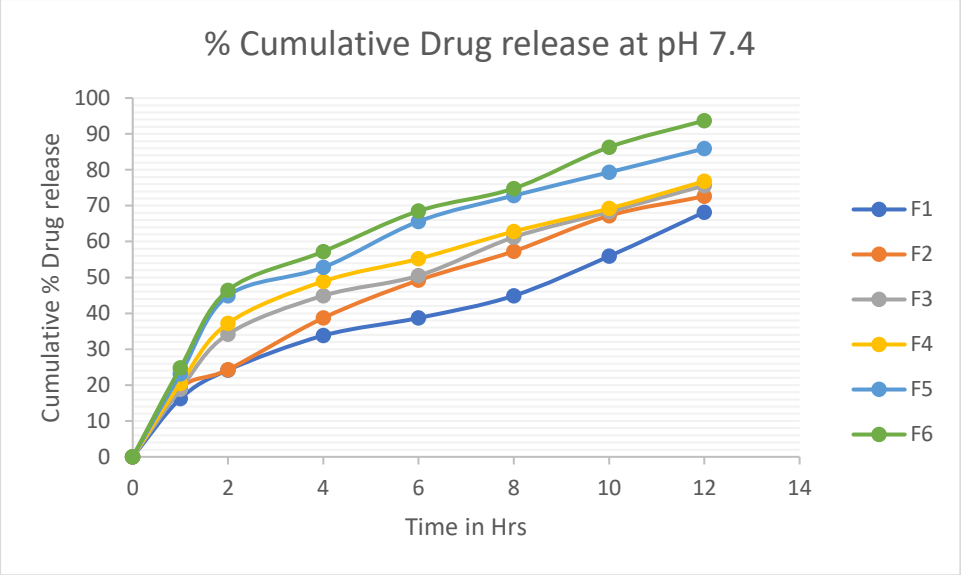
Table 14

Percentage cumulative drug release of orlistat at pH 7.4

S.No	Time in Hrs	% Cumulative Drug Release					
		F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	1	16.2	19.1	18.8	20.4	23.1	24.8
3.	2	24.2	24.3	34.2	37.2	44.9	46.4
4.	4	33.8	38.7	44.9	48.9	52.8	57.2
5.	6	38.7	49.2	50.5	55.2	65.6	68.5
6.	8	44.9	57.3	61.2	62.8	72.8	74.8
7.	10	55.9	67.2	68.3	69.2	79.3	86.3
8.	12	68.2	72.6	75.6	76.8	85.9	93.7

Figure 8

Percentage cumulative drug release of orlistat at pH 7.4



In vitro drug release studies were performed in the simulated gastric fluid of pH 1.2 and simulated intestinal fluid pH 7.4 made of phosphate buffer. In simulated conditions it is observed that the drug was maintained in a sustained manner. The formulation containing higher concentration of Eudragit RSPO, the percentage drug release was more in the first 2 hours, When the concentration of polycaprolactone was increased in the microsphere the drug release was maintained in a continuous fashion. The similar kind of effect was reported by jeong et.al. in his work. It is due to the fact that the Eudragit microsphere were more porous and drug release was rapid from it. In the formulation F1 & F2 containing higher amount of Eudragit RSPO 80 percentage of drug was released during first 6 hours. The other for formulations release the drug in a sustained manner up to 12 hours. when the concentration of Eudragit RSPO was decreased the drug release also extended. The Figure 7 and 8 represent the in vitro drug release all formulations in buffer solution of pH 1.2 and pH 7.4. Eudragit RSPO have low swelling ability at higher pH, hence it could not release the drug in extended manner. The formulation F4 (50:50) Showed excellent sustained release pattern in both pH 1.2 and pH 7.4 as compared with other ratios. This may be due to the good solubility of Eudragit RSPO and good swelling property of polycaprolactone in both the pH condition.

Conclusion

Orlistat loaded with Eudragit RSPO and polycaprolactone microparticles were successfully formulated using o/w solvent evaporation method. The recovery of microparticles, swelling index and in vitro floating ability where affected by changing the ratio of polymers. rheological properties visualise that the prepared microparticles were free flowing. In vitro buoyancy test prove that the formulated microparticles were hollow and floating above the surface of the simulated gastric fluid. In vitro drug release study showed that this formulation of microparticles can release the drug up to 12 hours in the simulated gastric condition. it is evident from the in vitro drug release study that the almost 70 percentage of drug were released from all the formulation. The formulation F4 Hence the formulation F4 was found to be possess best floating as well as sustained drug delivery system.

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Authors contribution statement

V.Vivekanandhan conceptualized and gathered the data about this work. Dr. D Kumudha organized these data, and all necessary inputs were given towards the designing of the manuscript. Both authors discussed the methodology, results and contributed to the final manuscript.

CONFLICT OF INTEREST

Conflict of interest declared none

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