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Formulation and evaluation of orlistat loaded microsponges for the treatment of obesity

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ABSTRACT:
The purpose of this study was to design novel drug delivery system containing orlistat micro sponges. Microsponges containing orlistatand Ethyl cellulose/ EudragitRS 100prepared by quasi emulsion solventdiffusion(Technique) method. The formulations were prepared step by step increases Drug: polymer ratio. The particle size (Malvern analyzer), Surface Morphology and structure examination (SEM) Production yield, Drug entrapmentEfficiency and in vitro drug release studied of microsponges were examined. Shape or surface morphology and topography of the orlistat microsponges were examined by scanning electron microscopy. The drug orlistat disperse in GIT for better therapeutic effect as microsponges disperse freely in GIT. To improve absorption of orlistat so as to enhance bioavailability, micro sponges is used as delivery systems which show better absorption and bioavailability then other dosage form of orlistat. The particle size were prepared microsponges was observed in the range of50.45 ± 0.85µm to 57.77 ± 1.35µm.The drug entrapment of the orlistat microsponges was observed in the range of 73.23 ± 0.23 to 83.41 ± 1.17 % The in vitro drug release study of the microsponges over 8 hour range from 59.28 ± 0.41% to73.16 ± 0.89 %.The objective of this research work was to formulation and evaluation of orlistat loaded microsponges for management of obesity disease.Microsponges drug delivery system landscape have been highly and rapidly evolving. They are allowing for novel product form. This delivery system are being integrated to optimize the efficacy or freestreaming effectiveness treatment.

Keywords: Microsponges, Enhance bioavailability, orlistat, Eudragit RS-100

I. INTRODUCTION:

As per WHO - Overweight and obesity are defined as abnormal or inordinate fat aggregation that presents a hazard to health.[1] A crude population measure of obesity is the body mass index (BMI), a person's (an individual's) weight (in kilograms) divided by the square of her or his height (in meters).Obesity disease is a neurotic condition in which the excess body fat collection, leading adverse side effects on health and healthy life expectancy.[2]

Obesity is now a global problem and is associated with a number of chronic conditions including osteoarthritis, gallstones, reproductive, fatty liver disease and gastrointestinal cancers, hypertension, heart failure, type 2 diabetes, coronary artery disease, stroke and coronary artery disease.[3]

The firstlytreatment for obesity is eating-less junk food and physical exercise. To supplement in case of failure, anti-obesity drugs may be taken to minimum appetite or increase fat absorption.

Microsponges are polymeric delivery systems composed of porous microspheres. They are small like (circular) sponge particles with a large (permeable) porous surface.[4] Microsponges are porous, polymeric microspheres that are utilized mostly for topical use and have recently been used for oral administration.[5] They are desire to deliver Active Pharmaceutical Ingredients efficiently at the lower dose and also to increases stability, modify drug release and decreases side effect.[6] Microsponge is recent latest novel technique for control release, non-harmful or non allergic and target specific drug delivery system. [7]

The aim of the present research work is formulation and evaluation of orlistat loaded microsponges for the treatment of obesity. Orlistat was formulation in the form of microsponges because microsponges disperse freely in the GIT, they are improve maximize drug absorption, increase bioavailability and minimum potential side effects.To improve absorption of orlistat so as to enhance bioavailability, microsponges is used as delivery system which show better absorption and bioavailability then other dosage form of orlistat.

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Orlistat microsponges can be prepared using the quasi emulsion solvent diffusion method. This method eliminates dust during formulation and yields high quality microsponges.

II. MATRIAL AND METHOD:

Materials:

Orlistat was gifted by Sun Pharmaceutical Pvt. Ltd. Dewas Madhya Pradesh India. Eudragit RS-100 was received from Evonic Degussa Privet limited Mumbai India. Ethyl cellulose and Poly vinyl alcohol received from shree ji polymer Ujjain Madhya Pradesh. Tri-ethyl-Citrate purchased by Himedia laboratories Pvt. Ltd, India. And all solvent and chemical use during formulationwas of analytical grade.

Method:

Orlistat loadedmicrosponges were prepared by quasi emulsion solvent diffusion (Technique) method. In this method, internal phase: Polymer Eudragit RS 100 / Ethyl cellulose was dissolved in 5 ml of ethanol. Orlistat was added and mixed well until it gets dissolved completely in under Ultrasonication at 35^0 Cand to which tri-ethyl citrate 2 ml was added to facilitate plasticity (used as Plasticizer).

External phase: Accurately weighed Poly vinyl alcohol was added to distilled water to form clear solution. Then internal phase was added drop wise (used micro pipette)in external phase. The mixture was stirred 1000 RPM for 2-3 hours, at Room Temperature. ThenMicrosponge were filtered by what-mann filter paper and dried at room temperature for 24 hour. All the 6 formulation of orlistat loaded microsponges of different drug: polymer ratios were prepared.[8, 9] **(Table 1)**

Table 1: Formulation chart of orlistat loaded microsponges

S No	Formulation code	Orlistat (mg)	Eudragit RS-100 (mg)	Ethyl cellulose (mg)	Poly Vinyl Alcohol (mg)	Tri-ethyl-citrate (ml)	Ethanol (ml)
1	F-1	100	100	-	100	2	5
2	F-2	100	200	-	200	2	5
3	F-3	100	300	-	300	2	5
4	F-4	100	-	100	100	2	5
5	F-5	100	-	200	200	2	5
6	F-6	100	-	300	300	2	5

MICROSPONGES CHARACTERIZATION:

Particle size analysis

Determination of the average particle size of orlistat loaded microsponges was determined using particle size analyzer (Malvern mastersizer, Hydro. 2000. UK). Orlistat microsponges were dispersed in double distill water before the running sample (microsponges) in the system to insure light scatterings signal (indicate by microsponges particle counted by per second) within the range of the system (with room temperature) the average particle size was analysis.[10]

Morphology Study Using Scanning Electron Microscope (SEM)

The internal and outside of morphology and surface topography can be studied by scanning electron microscopy (SEM) by sapience bioanalytical research lab Bhopal. Prepared microsponges can be covered with gold– palladium under an argon environment at room temperature and then SEM pictureof microsponges were recording the necessary magnification. SEM of a broke microsponges particle can also be taken to represent its ultra-structure.[11]

Determination of Production Yield

The prepared orlistat loaded microsponges of all formulation were accurately weighed. The measured weight of prepared microsponges (last weight) was divided by the total amount of all the excipients and drug used in the preparation of the microsponges, which give the total (raw material) percentageyield of orlistat microsponges. It was Production yield calculated by following equation.[12, 13]

$$\% \text{ Production Yield} = \frac{\text{Practical yield}}{\text{Theoretical yield (excipient + drug)}} X100$$

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Determination of drug entrapment

The microsponges drug entrapment was determined by UV spectrophotometrically (λ max = 207 nm). A sample of crushed orlistat microsponges(50 mg) was dissolved in 100 ml of 0.1 N HCL and (12 hour) kept for overnight. The drug content (entrapment) was determined and expressed as real drug content in microsponges. The drug entrapment efficiency (%) of the microsponges was calculated according to the following equation,[14]

$$\text{Drug entrapment} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \text{X } 100$$

In-vitro drug release study

The in vitro drug release of orlistat microsponges was studied using dissolution USP paddle type-II apparatus.The dissolution test was performedmicrosponges were carried out by filling equivalent amount of microsponges in pack in (muslin cloth) placed in the basket containing medium pH 0.1 N HCL 900ml (Simulated Gastric fluid) was used as medium with a stirring rate of 50 rpm. The temperature was maintained at 37^0 C ± 0.5^0C drug release was carried out in simulated gastric fluid. An aliquot of 5ml was collected sample (Using pipette) over a period of 8 hour and drug release determined by Ultra violet spectroscopy (Shimazdu-1800 Japan) for the drug λ max at 207nm.[15]

III. RESULTS AND DISCUSSION:

Physical appearance

The orlistat Microsponges particles are pure white, with generally excellent flow properties.

Particle size

Particle size of microsponges was determined using (Malvern mastersizer, analyzer. Hydro- 2000.UK.) Particle size analyzer average size of microsponges was determined in all batches. The formulation-1 to formulation -3 drug: polymer ratio (orlistat: Eudragit RS-100) show the average particle size range of 56.14 ± 0.07µm to 53.92 ± 0.75µm and the formulation-4 to formulation-6 drug: polymer ratio (orlistat: Ethyl cellulose) show the average particle size in range of 57.77 ± 1.35µm to 50.45 ± 0.85µm. It was observed the starring rate RPM was increases the particle size are decreases. The all formulation of mean particle size values were given in table-2.

Surface morphology and topography (SEM)

The internal and outside of morphology and surface topographyof the orlistat loaded microsponges were observed in scanning electron microscopy (SEM) by sapience bioanalytical research lab Bhopal M.P.. All the microsponges 'samples were covered with gold palladium alloy under vacuum. Covered Microsponges were examined using Zeises DSM, 982-SEM analyzer. The dried microsponges samples were put on NEM TAPE adhesive paper and SEM image of microsponges shown in figure-1

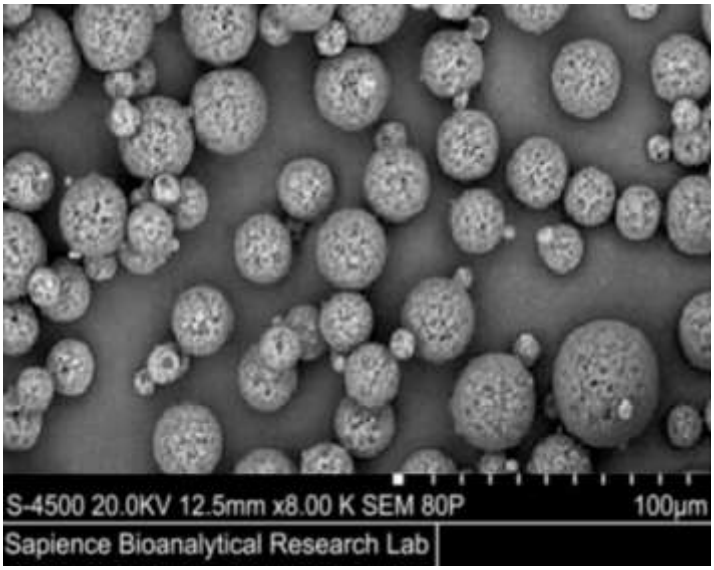

Figure-1: SEM photograph of microsponges formulation-3

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Determination of Production Yield

The prepared orlistat loaded microsponges of all batches were the total percentage production yield of microsponges given in table-2. It was found to be drug polymer ratio increases the production yield of increased. The all formulation F-1 to F-6 shows the production yield value of 70.23%, 72.59%, 84.28%, 80.54%, 82.36% and 81.42% respectively.

Determination of drug entrapment

The drug entrapment efficiency of orlistat loaded microsponges of all formulation is given in table-2. The drug content in different formulation was estimated by ultra-violet spectroscopy method. The drug entrapment depend on the successfully molecular association the drug with polymer.

The entrapment efficiency drug: polymer ratio (orlistat: Eudragit RS-100) form formulation-1 to formulation-3 range between 74.61%, 74.46%, 83.41% and Drug polymer ratio(orlistat: ethyl cellulose) form formulation-4 to formulation-6 ranges between 73.23%, 78.65%, 79.01%. The best drug entrapment efficiency was found in the formulation-3 and formulation -6 with drug polymer ratio 1:3 respectively. And Polymer Eudragit RS-100 with orlistat drug formulation-3 in very good drug entrapment efficiency.

Table-2: Particle size, Production yield, Drug entrapment and Percentage drug release of various microsponges' formulation.

S. No	Formulation code	Particle size µm (mean± S.D)	Production yield (%) (mean± S.D)	% Drug Entrapment (mean± S.D)	% Drug Release (mean± S.D)
1	F-1	56.14 ± 0.07	70.23 ± 0.75	74.61 ± 1.32	60.10 ± 0.34
2	F-2	54.14 ± 0.93	72.69 ± 1.64	78.46 ± 0.19	64.08 ± 1.56
3	F-3	53.92 ± 0.75	84.28 ± 0.73	83.41 ± 1.17	73.16 ± 0.89
4	F-4	57.77 ± 1.35	80.54 ± 0.93	73.23 ± 0.23	59.28 ± 0.41
5	F-5	56.66 ± 0.68	82.36 ± 1.26	78.65 ± 1.35	65.70 ± 0.54
6	F-6	50.45 ± 0.85	81.42 ± 2.10	79.01 ± 0.91	70.38 ± 0.73

In vitro drug release study

It was observe the drug release increase with increase drug polymer ratio. The microsponges dissolution rate are inversely related to particle size would be expected from surface area relationship. The drug polymer ratio increases concentration of polymer the increased drug encapsulation efficiency. It was found after 8 hour of dissolution studies the formulation f-1 to f-6 were show 60.10%, 64.08%, 73.16%, 59.28%, 65.70%, 70.08% of drug release in 8 hour. The formulation-3 (Drug: polymer ratio 1:3) orlistat: Eudragit RS-100 show better result 73.16% drug release then other formulation.

Table-3: In-vitro drug release profile of all microsponges formulation.

S. No	Formulation code	Cumulative % Drug release							
		1Hr	2 Hr	3Hr	4Hr	5Hr	6Hr	7Hr	8 Hr
1	F-1	7.86	14.15	20.45	27.13	39.52	46.33	55.75	60.10
2	F-2	11.07	15.84	23.58	29.53	39.15	46.42	56.08	64.09
3	F-3	14.46	23.13	30.73	39.51	45.63	54.33	63.27	73.16
4	F-4	9.09	12.23	22.32	26.33	36.01	44.71	51.23	59.28
5	F-5	10.56	15.27	18.35	30.33	41.58	48.86	58.68	65.70
6	F-6	12.77	20.73	29.60	39.22	46.35	52.02	61.65	70.38

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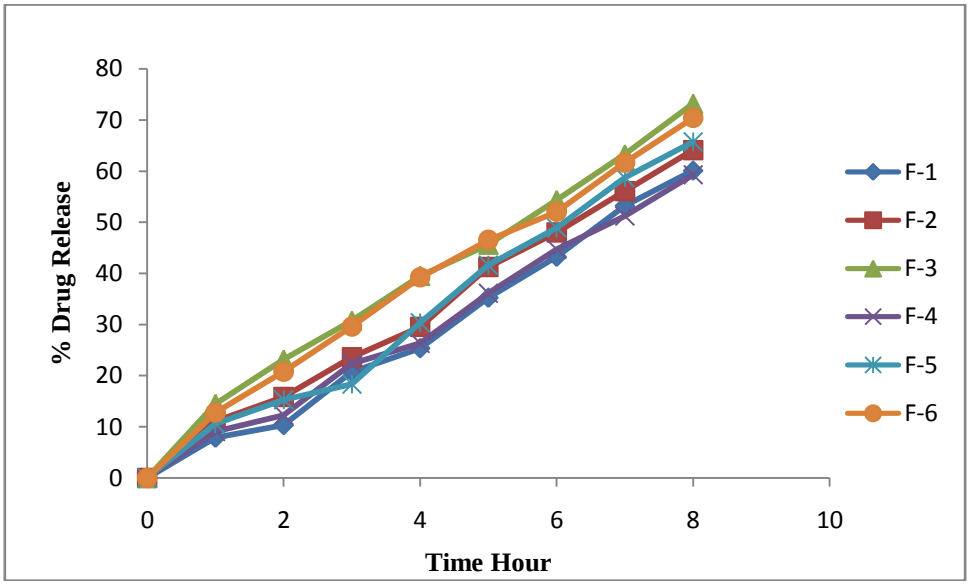

Figure-2: In-vitro drug release profile of (orlistat: Eudragit RS-100) microsponges F-1 to F-3 and (orlistat: Ethyl cellulose) microsponges F-4to F-6

IV. CONCLUSION:

In this research work orlistat is a poorly soluble drug with short half -life, thus selected as model drug for novel drug delivery system. To improve absorption of orlistat so as to enhance bioavailability, microsponges is used as delivery system which show better absorption and bioavailability then other dosage form of orlistat. Orlistat is formulated as Microsponges by Quasi emulsion solvent diffusion method using polymers Eudragit RS 100/Ethyl cellulose and Poly vinyl alcohol. This method found to be easy and rapid method.

The prepared orlistat microsponges formulation were evaluated production yield, drug entrapment andin-vitro drug release studied. In this formulation observed that drug: polymer ratios are increased production yield and drug entrapments are increased. Than starring rpm was increased the particle size are decreases and uniform spherical microsponges were prepared.All the microsponges formulation show uniform drug content and the formulation F-3 and F-6 show better in-vitro drug release.

The best formulation was found to be formulation-3 (drug: polymer ratio) orlistat: Eudragit RS-100 in this formulation good particle size 53.92 ± 0.75µm or better drug entrapment was found to reach up-to83.41 ± 1.17% and best percentage drug release 73.16 ± 0.89 from microsponges formulation compare to other formulation.

It was concluded microsponges as a best dosage form for oral drug delivery and microsponges are porous nature to provide better drug release in GIT.

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