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Formulation and evaluation of floating microspheres of lovastatin using Eudragit-E and ethyl cellulose by solvent evaporation method

Kapil Kumar Purohit[1]*, Navneet Garud[2]

1. Research Scholar, School of Studies in Pharmaceutical Science, Jiwaji University, Gwalior
2. Associate Professor, School of Studies in Pharmaceutical Science, Jiwaji University, Gwalior

ABSTRACT

Hollow multi-unit microspheres were prepared by a solvent diffusion technique in emulsion with a drug and an acrylic polymer. These were dissolved in a mixture of ethanol-dichloromethane and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the ratio of polymer to drug. The microballoons were floating in vitro for 12-24 hours when submerged in aqueous media. Radiographic studies showed that microballons administered orally to humans were dispersed in the upper part of the stomach and were held there for 3 hours against peristaltic movement. Floating Microspheres of Lovastatin were formed by Solvent Evaporation method .The formulas LV7 of Lovastatin Floating Microspheres shows a very good drug release profiles and shown better sustained action till the end of last hour (24th hrs). It will improve patient compliance and increase in bioavailability which give better approach to treat hypertensive condition and the antihyperlipidemic action of Lovastatin lower the long term complications of Hypertension and reduce the risk of heart failure, CHF, Myocardial Infarction and also vascular damage in blood vessels and kidney.

Keywords: Lovastatin, Floating microspheres, Drug Entrapment, In-vitro drug release.

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***Address for Correspondence:**

Mr. Kapil Kumar Purohit, Research Scholar, School of Studies in Pharmaceutical Science, Jiwaji University, Gwalior

INTORDUCTION[1]

Microencapsulation is one of the quality preservation techniques of sensitive substances. This is the method for producing content with new valuable assets. Microencapsulation is the process of enclosing micron-size particles in a polymer shell. Various techniques are available for encapsulation of pharmaceutical units. The encapsulation efficiency of micro particle or microscopy or microcapules depends on the concentration of polymer, solubility of polymer in solvent, solvent removal rate, solubility of organic solvent in water, and so on. Microencapsulation is described as the process of enclosing micron size, particles of solids or droplets of liquids or gases in a passive shell, which in turn separates them from the external environment and protects them. The product obtained by this process is called microtecticle, microcapsule, microscopy, which differentiate into morphology and internal structure. When the particle size is below 1µm then particles between nanoparticles, nano capsules, nanoscopes, 3 to 800 microns respectively, are known as microprotection or microcrypsule or microscopy. The particle larger than 1000 microns is known as macro particles.

Floating systems[2,3]:

These have a bulk density lower than the gastric content. They remain floating in the stomach for a prolonged period of time, with the possibility of a continuous release of the drug. Eventually, the residual system empties from the stomach. Gastric emptying is much faster in the fasting state, and floating systems rely heavily on the presence of food to delay emptying and provide sufficient fluid for effective buoyancy.

Hollow Floating Microspheres:

Hollow multi-unit microspheres were prepared by a solvent diffusion technique in emulsion with a drug and an acrylic polymer. These were dissolved in a mixture of ethanol-dichloromethane and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the ratio of polymer to drug. The microballoons were floating in vitro for 12-24 hours when submerged in aqueous media. Radiographic studies showed.

hat microballons administered orally to humans were dispersed in the upper part of the stomach and were held there for 3 hours against peristaltic movement.

Advantages and Disadvantages of FDDS

- **Advantages of FDDS:**

• Drugs that act locally in the stomach, e.g. antacids, antibiotics for the microbial ulcer, etc.

• Drugs that are absorbed mainly in the stomach e.g. Albuterol

• Drugs those are poorly soluble at alkaline pH.

• Drugs that have a narrow absorption window for the absorption of medicines that are absorbed from the proximal part of the small intestine. e.g. Riboflavin, Levodopa, PABA. Medications that degrade in the colon e .g. Captopril, metoprolol

- **Disadvantages of FDDS:**

• High variability in gastric emptying time due to variations in the emptying process.

• Drugs that cause irritation and injury to the gastric mucosa and unstable gastric fluid cannot be formulated as FDDS

• Drugs with unpredictable bioavailability, minimum effective concentration are achieved slowly.

MATERIALS AND METHODS:

- **Materials and Equipment**

Materials Used For Lovastatin Microspheres

S. No	Chemical Name	Supplier
1	Lovastatin	Micro labs, Pvt, Ltd Bengaluru (Gift Sample)
4	Ethyl Cellulose	Lobachemi, Pvt Ltd.Mumbai
5	Eudragit E	Lobachemi, Pvt Ltd.Mumbai
7	Ethonol	S.D fine chemicals Pvt Ltd, Mumbai
8	Methenol	S.D fine chemicals Pvt Ltd, Mumbai
9	Dichloromethane	Merck Pvt Ltd, Mumbai
10	Conc.HCL	Nice chemicals, Pvt Ltd, Cochin
11	Tween 80	S.D fine chemicals Pvt Ltd, Mumbai

Table 1: Materials Used For Lovastatin Microspheres

- **Equipments Used**

S.No	Name of the Equipment	Supplier
1	Pippetes,Beakers	Borosil
2	Hot air oven	Sunbim manfacture Pvt. Ltd
3	Uv-spectro photo meter	Shimadzu
4	Dissolution apparatus	Electro lab
5	Magnetic stirrer	Sunsim, India
6	PH meter	Elico
7	Scanning eletron microscopy	JEOL, JSM-670F,Japan
8	sieve	Jayanth scientific IND, Mumbai
9	FT –IR apparatus	Shimadzu

Table 2: Equipment Used For Lovastatin Microspheres

Methodology

1. Preformulation Studies

A. FT-IRStudies[4]:

- **Lovastatin & polymers**

The FT-IR analysis was done conducted for the analysis of drug polymer interaction and stability of the drug during microencapsulation process. The FT-IR spectrum of pure lovastatin, Eudragit E, ethyl cellulose, was studied. The physical mixtures of the floating microspheres formulation also were recorded.

3. **Formulation of lovastatin floating microspheres** Lovastatin loaded microspheres were prepared by solvent evaporation technique. Ethyl cellulose and Eudragit E was dissolved in a mixture of methanol and dichloromethane at room temperature. Lovastatin was added to above solution and then it was stirred on a magnetic stirrer to form a homogenous solution. Then the above solution was poured into 100 ml of water containing 0.01% Tween 80 maintained at room temperature. The mixture was stirred for three hour. The microspheres were separated by filtration and then dried at room temperature. The formulation plan is described in Table.

Table 3: (a): Levels and the experimental condition for the 3^2 factorial design

S. No.	Factors	Low level (-)	Mid level (0)	High level (+)
1	Polymer concentration (Eudragit E : Ethyl cellulose) (%w/v)	0.25:0.50	0.37:0.75	0.5:1.00
2	Solvent ratio Ethanol : Dichloromethane (%v/v)	1:1	1.5:1	2:1

(b) Formulation of microsphere by implementing 3^2 factorial designs

Formulation code	X1 (Independent Variable)		X2 (Independent Variable)	
	Actual Value	Code value	Actual Value	Code value
LV1	0.25:0.50	-1	1 : 1	-1
LV2	0.25:0.50	-1	1.5 : 1	0
LV3	0.25:0.50	-1	2 : 1	1
LV4	0.37:0.75	0	1 : 1	-1
LV5	0.37:0.75	0	1.5 : 1	0
LV6	0.37:0.75	0	2 : 1	1
LV7	0.5:1.00	1	1 : 1	-1
LV8	0.5:1.00	1	1.5 : 1	0
LV9	0.5:1.00	1	2 : 1	1

X1= Polymer concentration (Eudragit E: Ethyl Cellulose) (%w/v)

X2=Solvent ratio Ethanol: Dichloromethane (%v/v)

Table 4: Optimization of Losartan microsphere formulation by implementing three level two factor factorial design.

Formulation code	Drug (mg)	Effect of Independent variables (X)		Responses of dependent variables (Y)			
		X1 (% w/v)	X2 (% v/v)	Y1 (Particle size in µm)	Y2 (% Buoyancy)	Y3 (% Drug entrapment)	Y4 (% Drug release)
LV1	500	0.25:0.50	1 : 1	623±1.02	60.22±1.43	57.6±1.03	99.5±1.37*
LV2	500	0.25:0.50	1.5 : 1	646±1.21	59.19±1.64	58.3±1.04	98.85±1.31*
LV3	500	0.25:0.50	2 : 1	672±2.32	59.10±1.78	59.4±1.50	97.26±1.63*
LV4	500	0.37:0.75	1 : 1	757±1.01	75.50±1.43	67.1±1.06	98.55±1.20**
LV5	500	0.37:0.75	1.5 : 1	775±1.05	71.90±1.11	69.6±1.05	96.98±1.33**
LV6	500	0.37:0.75	2 : 1	792±1.22	70.01±1.81	72.4±1.23	95.31±1.90**
LV7	500	0.5:1.00	1 : 1	700±1.42	82.98±1.94	82.2±1.74	96.57±1.92**
LV8	500	0.5:1.00	1.5 : 1	710±1.09	78.23±1.86	81.9±1.15	92.32±1.84***
LV9	500	0.5:1.00	2 : 1	730±1.23	76.54±1.32	80.3±1.27	90.13±1.63***

Note:- * - Drug release completed in 16 hrs ** - Drug release completed in 20 hrs *** - Drug release completed in 24 hrs

3. EvaluationTests:[5]

The following parameters are determined for floating microspheres of Lovastatin

- **Drug Entrapment:**[6]

The various formulations of the floating microspheres were subjected for drug content. 100mg of floating microspheres from all batches were accurately weighed. The microspheres were dissolved with 10ml ethanol in in 100ml volumetric flask and makeup the volume with 1.2 pH acidic buffer. The resulting solution is then filtered through whatmann filter paper no 44.after filtration, from the solution 10ml was taken out and diluted up to 100ml with pH1.2 .again from the solution taken out and diluted up to 10ml with pH1.2 and the absorbance was measured at 232nm against pH1.2 as blank. The percentage drug entrapment was calculated as follows.

$$\%\text{drug entrapment} = \frac{\text{calcuted drug concentration}}{\text{theoretical drug concentration}} \times 100$$

- **Particle size analysis:** [7,8]

Particle size analysis plays an important role in determining the release characteristic and floating property. The size of floating microspheres were measured by using an optical microscope, and the mean practical size was calculated by measuring nearly 200 particles with the help of calculated ocularmicrometer.

- **Percentae yield**[9]**:**

The prepared microspheres weighed from different formulations the measured weight was divided by the total amount of all non -volatile components which were used for the preparation of microspheres.

$$\text{percentage yeild} = \frac{\text{actual weight of product}}{\text{total weight of drug and polymer}} \times 100$$

- **Buoyancy percentage:** [10]

100 mg of floating microspheres were placed in pH1.2 (900ml) containing 0.02% of tween80.the mixture was stirred with paddle at 100 rpm. The layer of buoyant microsphere was pippeted and separated by filtration at 1, 2, 4, 6, 10, 16 and 24 hrs the collected microspheres were dried in desiccators overnight. The percentage of microspheres was calculated by the following equation:

$$\text{percentage floating microspheres} = \frac{\text{weight of floating microsphere}}{\text{intial weight of floating microsphere}} \times 100$$

.

- **Scanning electron microscopy:**[11]

Dry microspheres were placed on an electron microscope brass stub coated with gold in an ion sputter. Then picture of microsphere were taken by random scanning of stub. The SEM analysis of the microspheres was carried out by using JEOL, JSM-670F japan (Sastra University, tanjavur).the microspheres were viewed at an accelerating voltage of 3.0.

- ***In-Vitro* Drug release studies:**[12]

The drug release rate from floating microspheres was carried out using the USP type – II dissolution basket assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were discrete in 900 ml of pH1.2

maintained at 37±0.5 ºC and stirred at 50 rpm. 1ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium replaced in the vessel after each withdrawal to maintain sink condition. The collected samples were suitably diluted with pH 1.2 and analyzed spectrophtometrically at specific wavelengths to determine the concentration of drug present in the dissolution medium.

Details of dissolution test:

1. Apparatus : USP type II
2. Volume of medium : 900 ml
3. Temperature : 37 ± 0.5 °C
4. Paddle speed : 50 rpm
5. Dissolution medium used : 0.1 N HCl containing 0.02% tween 20
6. Aliquot taken at each time interval: 10 ml

RESULT AND DISCUSSION

Drug Entrapment

The drug Entrapment Efficacies of different formulations were in range of 57.6 - 82.2 % w/w.

Table 5: Drug Entrapment

Sr no.	Formulation	Drug entrapment (%)
1	LV1	57.6±1.03
2	LV2	58.3±1.04
3	LV3	59.4±1.50
4	LV4	67.1±1.06
5	LV5	69.6±1.05
6	LV6	72.4±1.23
7	LV7	82.2±1.74
8	LV8	81.9±1.15
9	LV9	80.3±1.27

All values are in the form of Mean ± SD where n= 3

Drug Entrapment

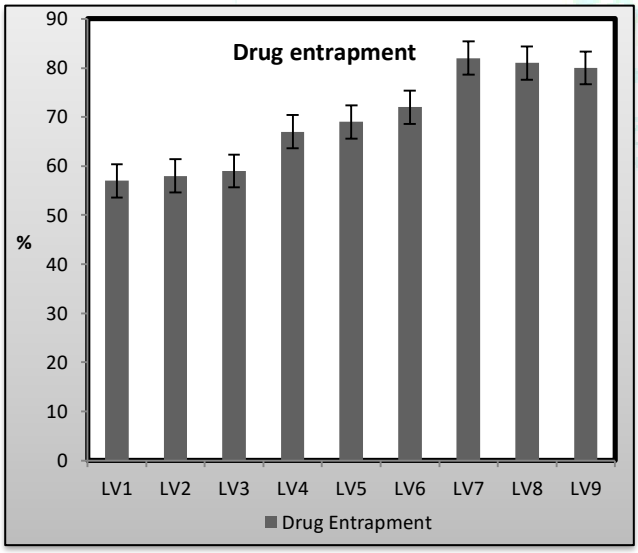

Fig 1: Drug Entrapment

Particle Size Analysis:

The particle size was determined by optical microscopy method. It plays an important role in floating ability and drug release.

Microspheres ranges between 500µm-1000µm, the floating ability will be more and release rate will be in sustain manner.

The mean particle size of microspheres was in range 623-792µm.the results were tabulated in the table .The particle size distribution was almost uniform and narrow in all the formulations.

Table 6: Particle Size Analysis

S. no	Formulation code	Mean particle size (µm)
1	LV1	623±1.02
2	LV2	646±1.21
3	LV3	672±2.32
4	LV4	757±1.01
5	LV5	775±1.05
6	LV6	792±1.22
7	LV7	700±1.42
8	LV8	710±1.09
9	LV9	730±1.23

All values are in the form of Mean ± SD where n= 3

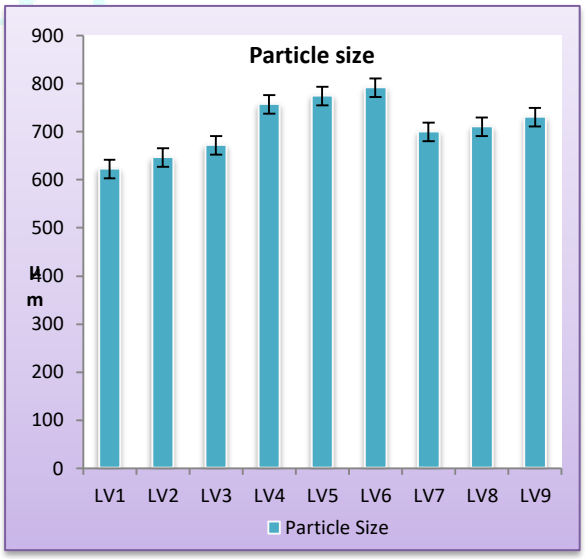

Fig 2: Particle Size Analysis

Percentage yield:

The percentage yield of different formulation was determined by weighing the microspheres after

Table 7: Percentage Yield

Sr. no	Formulation code	Percentage yield
1	LV1	64.2±1.43
2	LV2	62.8±1.42
3	LV3	61.8±1.67
4	LV4	53.3±1.25
5	LV5	55.2±1.77
6	LV6	59.7±1.11
7	LV7	83.8±2.10
8	LV8	77.7±1.01
9	LV9	79.1±1.41

All values are in the form of Mean ± SD where n= 3

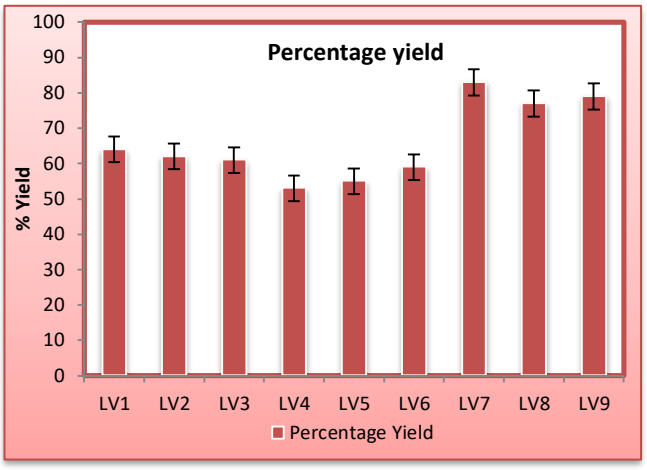

Fig. 3: Percentage Yield

Floating behavior of Lovastatin Microspheres:

Table 8: Floating behavior of Lovastatin Microsphere

Time (hrs.)	Floating behavior of lovastatin microspheres								
	LV1	LV2	LV3	LV4	LV5	LV6	LV7	LV8	LV9
1	94.61±1.91	91.35±1.66	90.13±1.33	96.39±1.87	95.23±1.14	97.16±1.33	98.12±1.93	95.719±1.45	93.23±1,17
2	88.05±1.86	85.74±1.63	84.09±1.64	94.11±1.32	91.73±1.25	90.19±1.23	95.19±1.76	91.19±1.53	89.23±1.19
4	81.82±1.74	79.94±1.56	78.71±1.98	90.76±1.76	87.84±1.37	85.02±1.54	90.23±1.68	88.11±1.29	87.44±1.61
6	76.79±1.24	73.96±1.91	72.91±1.65	86.19±1.61	83.20±1.33	81.33±1.32	88.21±1.63	86.29±1.43	83.82±1.87
10	69.93±1.56	68.71±1.87	66.47±1.04	83.34±1.34	78.65±1.63	77.68±1.62	86.27±1.98	83.43±1.39	80.22±1.09
16	63.81±1.76	62.87±1.90	60.68±1.45	80.73±1.26	75.17±1.87	73.75±1.76	84.33±1.20	80.43±1.61	78.22±1.70
24	60.22±1.43	59.19±1.64	59.10±1.78	75.50±1.43	71.90±1.11	70.01±1.81	82.98±1.94	78.23±1.86	76.54±1.32

All values are in the form of Mean ± SD where n= 3

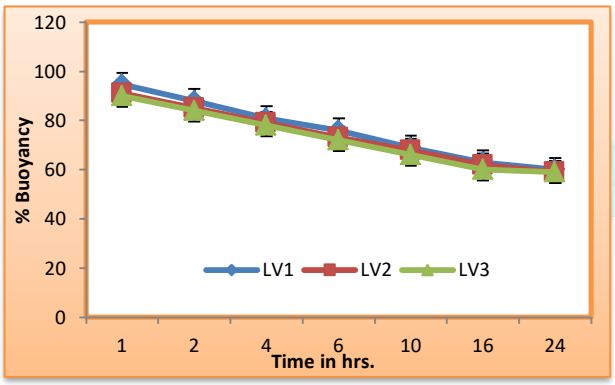

Fig 4: Floating behavior of Lovastatin Microspheres (All Formulations)

Scanning electronic microscopy:

Shape and surface characteristics of microspheres were examined by scanning electron microscopy. Surface morphology of LV4 formulation was examined at an different magnification of 400X and 2000X, which illustrate the smooth surface of floating microspheres and small hollow cavity present in microspheres which is responsible for floating property. SEM revealed. All the selected microspheres were smooth, almost spherical in shape and non-porous as well as hollow microsphere interior. The surface morphology internal structure of microspheres was determined by SEM as shown in figure.

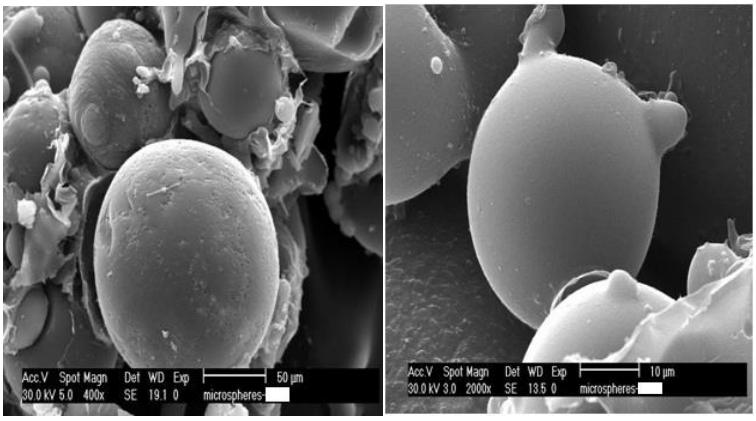

Fig 5: Scanning Electronic Microscopy of Lovastatin Microspheres

In-vitro drug release profile of lovastatin microspheres

The drug release data obtained for the formulations from LV1 –LV9 were tabulated in the table. The *in-vitro* release studies of the floating microspheres were studied for all the formulations. The cumulative percentage drug released from floating microspheres decreased with increase in concentration of polymers Eudragit E & Ethyl cellulose respectively.

Table 9: *In-vitro* Drug Release from Lovastatin Microspheres

Time (hrs.)	Cumulative percentage drug released								
	LV1	LV2	LV3	LV4	LV5	LV6	LV7	LV8	LV9
0	0	0	0	0	0	0	0	0	0
1	11.42±1.10	9.40±1.90	8.42±1.65	7.79±1.20	6.64±1.21	7.23±1.65	5.32±1.79	6.11±1.65	8.21±1.01
2	19.63±1.03	17.44±1.43	15.46±1.55	15.23±1.01	13.40±1.43	14.39±1.42	11.54±1.32	10.32±1.62	12.44±1.82
3	28.7±1.08	25.76±64	24.45±1.41	23.06±1.22	21.72±1.54	22.25±1.37	18.52±1.30	16.53±1.89	20.21±1.49
4	42.06±1.31	38.73±1.63	36.39±1.93	33.25±1.82	32.51±1.56	34.71±1.50	25.75±1.53	23.86±1.03	28.45±1.37
5	57.98±1.83	53.86±1.46	48.47±.1.91	44.44±1.20	40.12±1.87	43.22±1.43	33.21±1.87	34.19±1.07	38.34±1.43
6	68.10±1.12	62.95±1.66	58.39±1.92	53.52±1.10	49.14±1.53	50.16±1.32	38.31±1.22	41.44±152	44.10±1.26
8	81.10±1.54	76.65±1.32	73.25±1.77	68.63±1.31	62.78±1.92	63.76±1.39	46.31±1.32	47.40±1.09	51.77±1.93
12	99.5±1.37	98.85±1.31	97.26±1.63	83.56±1.42	78.43±1.32	76.42±1.20	56.23±1.44	59.54±1.50	61.22±1.45
16	99.5±1.37	98.85±1.31	97.26±1.63	98.55±1.20	96.98±1.33	95.31±1.90	72.77±1.87	75.89±1.40	70.10±1.59
20				98.55±1.20	96.98±1.33	95.31±1.90	84.21±1.51	80.19±1.26	78.11±1.30
24							96.57±1.92	92.32±1.84	90.13±1.63

All values are in the form of Mean ± SD where n= 3

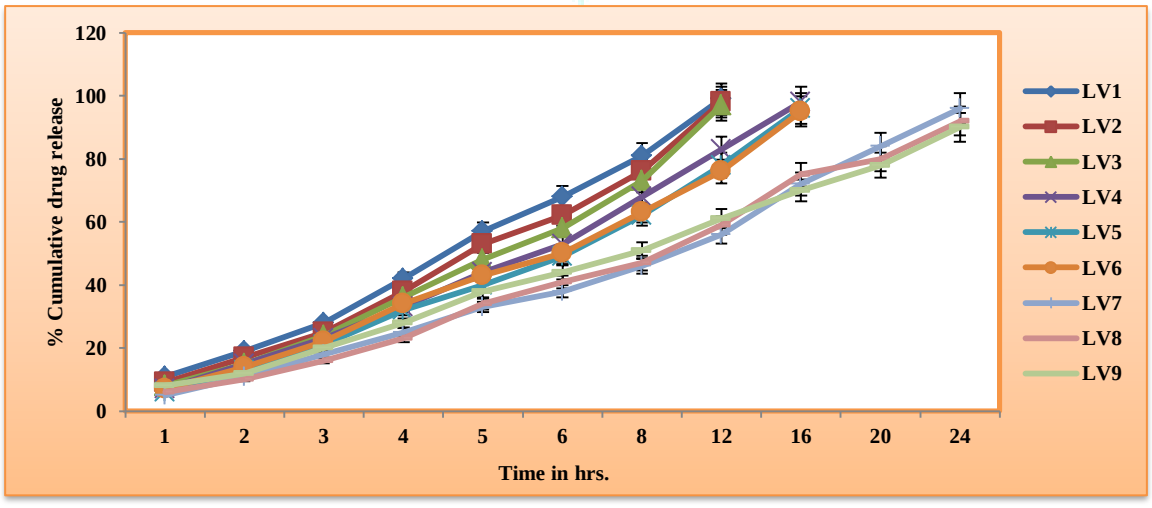

Fig 6: *In-vitro* Drug Release from Lovastatin Microspheres (All Formulations)

Optimization of LV7 formulation of lovastatin microspheres:

The formulation optimized by implementing 3^2 factorial designs. In this design the polymer concentration and solvent ratio using as Independent variable and the levels for formulations are Low, Medium and High. The dependent variables for studies are Particle size, Buoyancy, Drug entrapment and Drug release.

Table 10 Optimization of Release at 24th Hr

Regression statistics	
Multiple R	0.9993928
R Square	0.9987858
Adjusted R Square	0.996762
Standard Error	0.6950513
Observations	9

Table 11 Analysis of variance

ANOVA					
	Degree of freedom	Sum Square	Mean Square	F	Significance F
Regression	5	1192.1262	238.42524	493.53559	0.0001435
Residual	3	1.4492891	0.4830964		
Total	8	1193.5755			

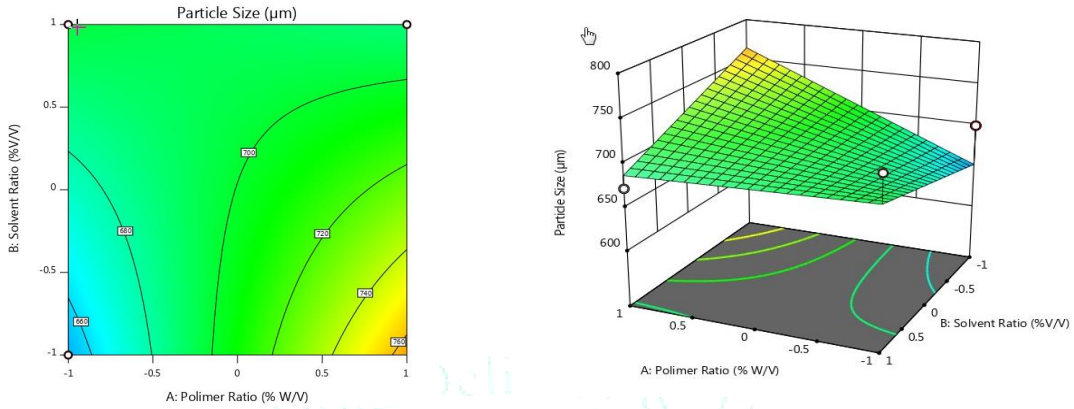

Fig 7: Contour Plot for Particle Size after Optimization

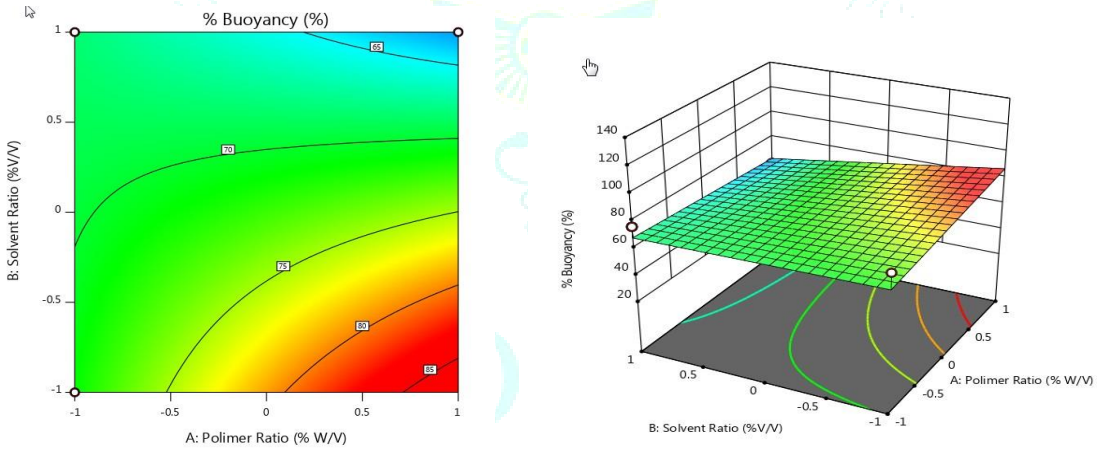

Fig 8: Contour Plot for Buoyancy after Optimization

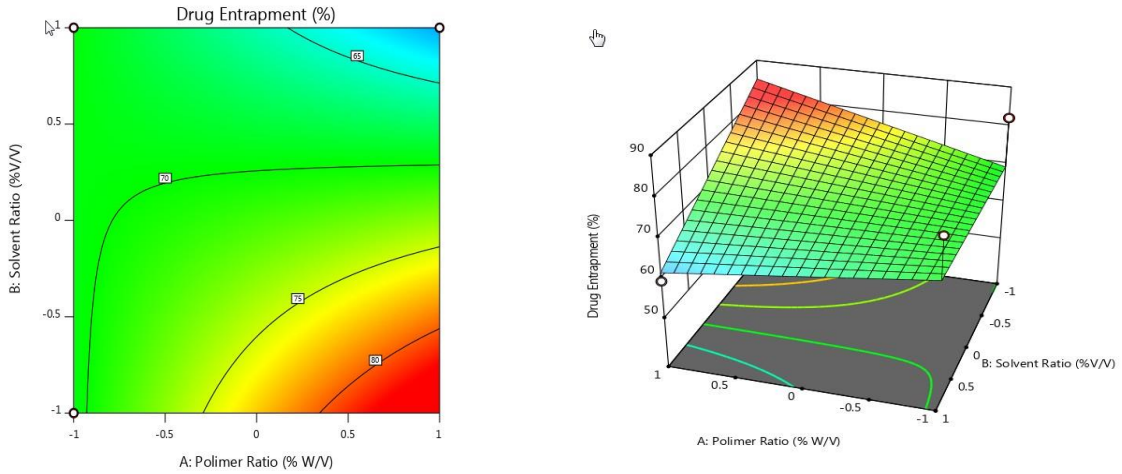

Fig 9: Contour Plot for % Drug Entrapment after Optimization

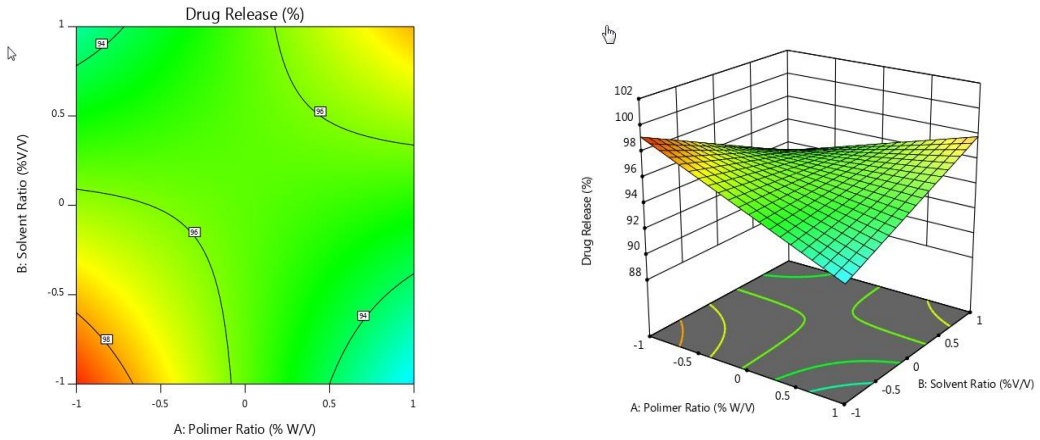

Fig 10: Contour Plot for % Drug Release after Optimization

CONCLUSION

It can be concluded that Floating Microspheres of Lovastatin were formed by Solvent Evaporation method .The formulas LV7 of Lovastatin Floating Microspheres shows a very good drug release profiles and shown better sustained action till the end of last hour (24th hrs). It will improve patient compliance and increase in bioavailability which give better approach to treat hypertensive condition and the angiotensin receptor blocking action of Losartan lower the long term complications of Hypertension and reduce the risk of heart failure, CHF, Myocardial Infarction and also vascular damage in blood vessels and kidney.

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