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Formulation and evaluation of floating microspheres of losartan potassium using sodium alginate and HPMC by solvent evaporation method

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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 Losartan potassium were formed by Solvent Evaporation method .The formulas LP7 of Losartan Potassium 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.

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

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INTORDUCTION

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[1].

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 of FDDS:

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

• Drugs that are absorbed mainly in the stomach, p. Eg Albuterol

• Drugs that 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 eg. 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 can not be formulated as FDDS

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

MATERIALS AND METHODS

Materials

Table 1: Materials Used For Losartan Potassium Microspheres

S. No	Chemical Name	Supplier
1	Losartan Potassium	Micro labs, Pvt, Ltd Bengaluru (Gift Sample)
4	Sodium Alginate	Lobachemi, Pvt Ltd.Mumbai
5	HPMC K 100	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

Equipments

Table 2: Equipment Used For Losartan Potassium Microspheres

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

Methodology

1. Preformulation Studies

A. FT-IR Studies[4]:

The FT-IR spectrum of pure Losartan, sodium alginate, HPMC K 100 was studied. The physical mixtures of the floating microspheres formulation also were recorded.

2. Formulation of Losartan Potassium Floating Microspheres

Losartan Potassium loaded Floating Microspheres were prepared by solvent evaporation technique. HPMC K100 and Sodium alginate was dissolved in a mixture of ethanol and dichloromethane (1:1) at room temperature. Losartan Potassium 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. Formulation plan described in Following 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 (Sodium alginate : HPMC K100) (%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

Table 3: (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
LP1	0.25:0.50	-1	1 : 1	-1
LP2	0.25:0.50	-1	1.5 : 1	0
LP3	0.25:0.50	-1	2 : 1	1
LP4	0.37:0.75	0	1 : 1	-1
LP5	0.37:0.75	0	1.5 : 1	0
LP6	0.37:0.75	0	2 : 1	1
LP7	0.5:1.00	1	1 : 1	-1
LP8	0.5:1.00	1	1.5 : 1	0
LP9	0.5:1.00	1	2 : 1	1

X1= Polymer concentration (Sodium alginate: HPMC K100) (%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)
LP1	500	0.25 : 0.50	1 : 1	675±11.13	68.98±1.26	55.2±0.21	97.03±1.92*
LP2	500	0.25 : 0.50	1.5 : 1	677±12.43	70.89±1.53	55.6±0.31	95.01±1.19*
LP3	500	0.25 : 0.50	2 : 1	689±11.45	69.12±1.62	56.1±0.34	93.31±1.02*
LP4	500	0.37 : 0.75	1 : 1	690±11.76	73.62±1.33	56.7±0.64	98.91±1.01**
LP5	500	0.37 : 0.75	1.5 : 1	710±11.32	76.56±1.20	58.3±0.29	97.09±1.20**
LP6	500	0.37 : 0.75	2 : 1	723±11.33	75.15±1.73	58.6±0.27	96.71±1.06**
LP7	500	0.5 : 1.00	1 : 1	740±11.92	84.87±1.25	66.2±0.28	98.34±1.03***
LP8	500	0.5 : 1.00	1.5 : 1	745±10.32	80.23±1.24	61.2±0.22	95.12±1.06***
LP9	500	0.5 : 1.00	2 : 1	772±12.11	82.98±1.63	59.2±0.26	93.34±1.09***

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 Losartan Potassium

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 make up the volumewith1.2 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 362nm 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.

Percentage 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 over night. 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 55.2 - 64.2%w/w.as shown in the figure 1. Drug entrapment efficacy slightly decreased with increase HPMC K100 content ratio in microspheres. This is due to the permeation characteristic of HPMC K100 that could facilitate diffusion of part of entrapped drug to surrounding medium during preparation of floating microspheres.

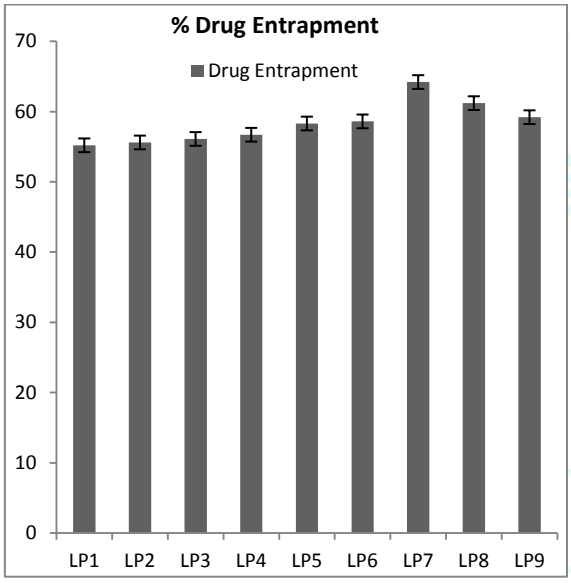

Figure 1: Drug Entrapment

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 sustaining manner.

The mean particle size of microspheres was in range 675-772 µm. The results were shown in the figure 2. The particle size distribution was almost uniform and narrow in all the formulations.

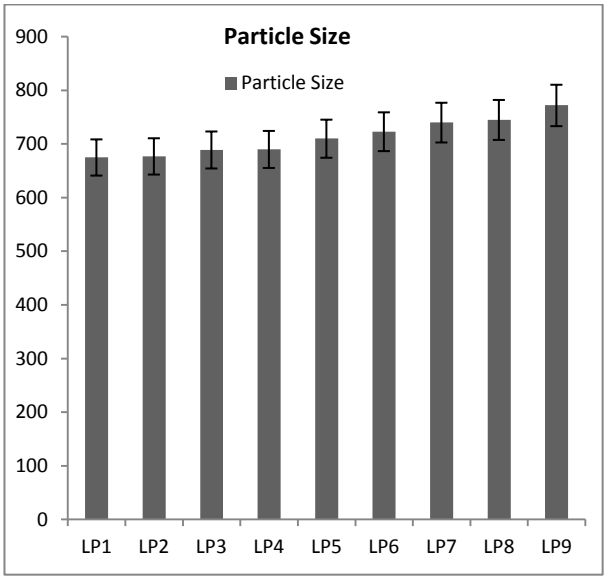

Figure 2: Particle Size Analysis

Percentage Yield:

The percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of developed formulations of Losartan Potassium floating microspheres LP1-LP9 were found to be in the range of 53.7 -78.3%.

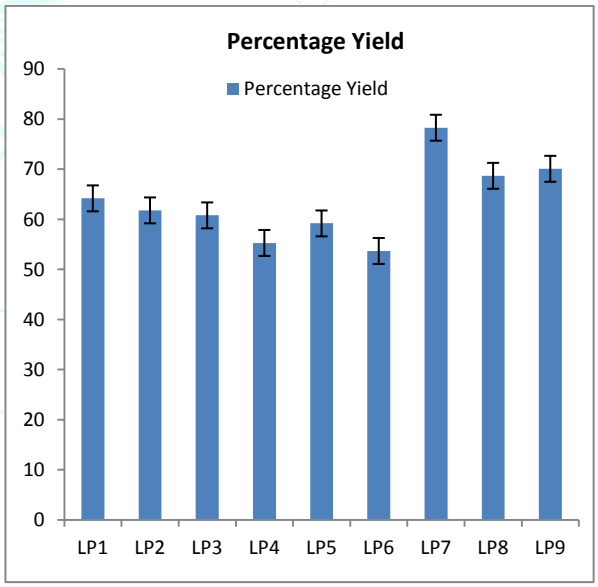

Figure 3: Percentage Yield

Floating behavior of Losartan Potassium Microspheres:

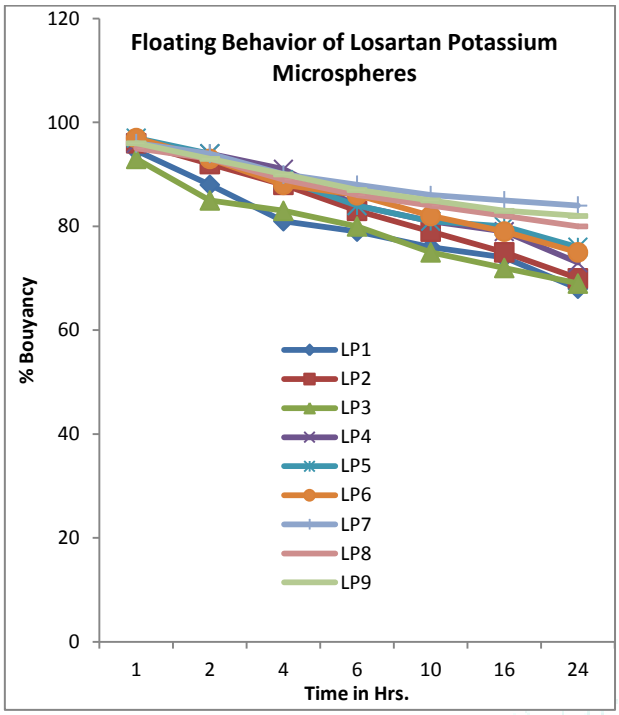

Figure 4: Floating behavior of Losartan Potassium Microspheres (All Formulations)

Scanning Electronic Microscopy:

Shape and surface characteristics of microspheres were examined by Scanning Electron Microscopy. Surface morphology of LP7 formulation was examined at an different magnification of 100X and 500X, which illustrate the smooth surface of floating microspheres and small hollow cavity present in microspheres which is responsible for floating property. SEM revealed pores on the microsphere as well as hollow microsphere interior. The surface morphology internal structure of microspheres was determined by SEM as shown in figure 5. From this figure it was observed that so many pores are formed due to the drug release. Some pores may be small on big in size due to the blasting of the drug.

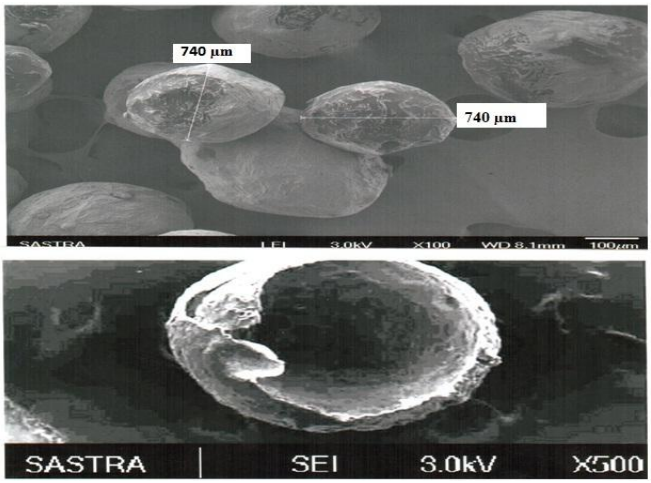

Figure 5: Scanning Electronic Microscopy of Losartan Potassium Microspheres

In-vitro Drug Release Profile of Losartan Potassium Microspheres:-

The drug release data obtained for the formulations from LP1 –LP9 were shown in figure 6. The *in-vitro* release studies of the floating microspheres were studied for all the formulations.

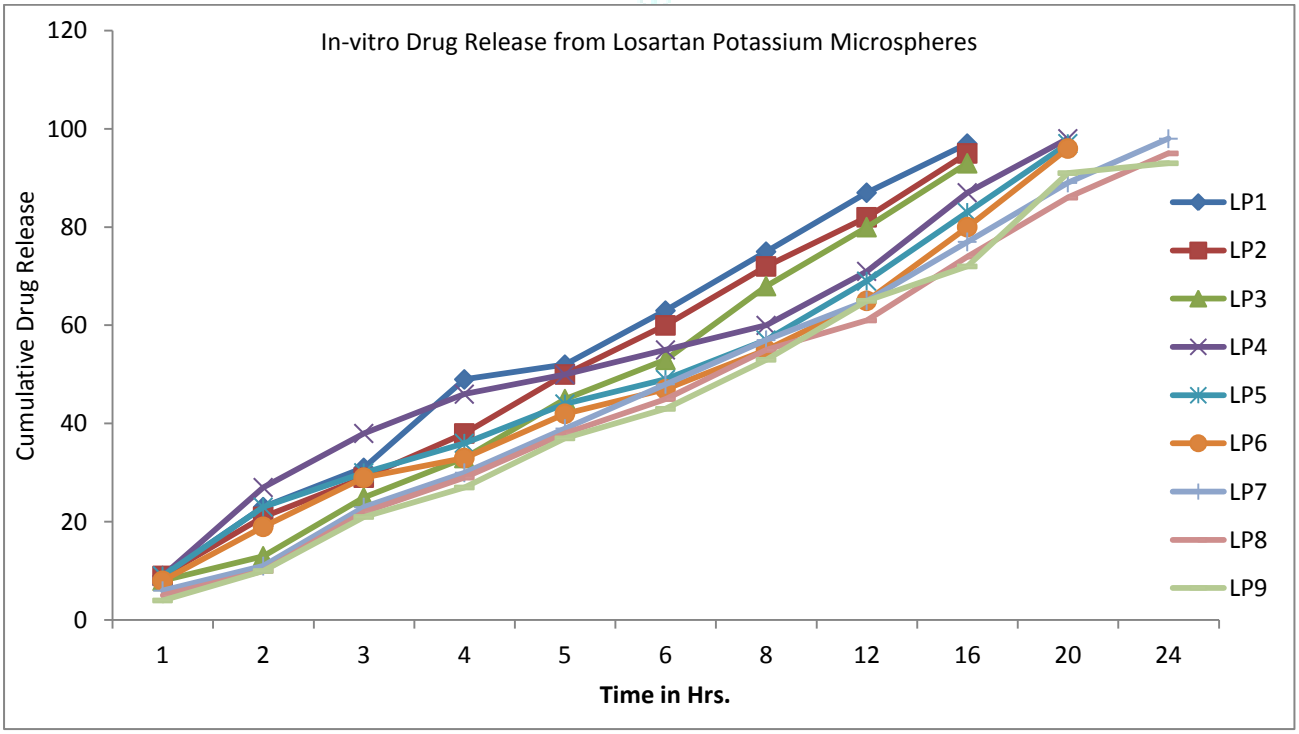

Figure 6: *In-vitro* Drug Release from Losartan Potassium Microspheres (All Formulations)

Table 5: Optimization of Release at 24th Hr

Regression Statistics	
Multiple R	0.9995927
R Square	0.9983858
Adjusted R Square	0.996462
Standard Error	0.6976513
Observations	9

Table 6: Analysis of variance

ANOVA					
	Degree of Freedom	**Sum Square**	**Mean Square**	**F**	**Significance F**
Regression	**5**	1152.1262	246.42524	499.53559	0.0001835
Residual	**3**	1.6592891	0.5730964		
Total	**8**	1181.5755			

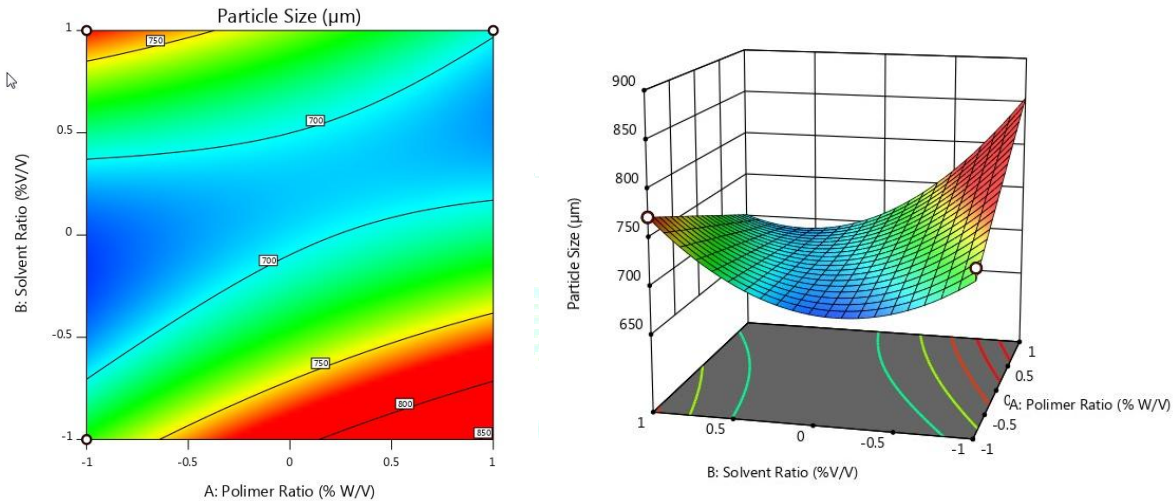

Figure 7: Contour Plot for Particle Size after Optimization

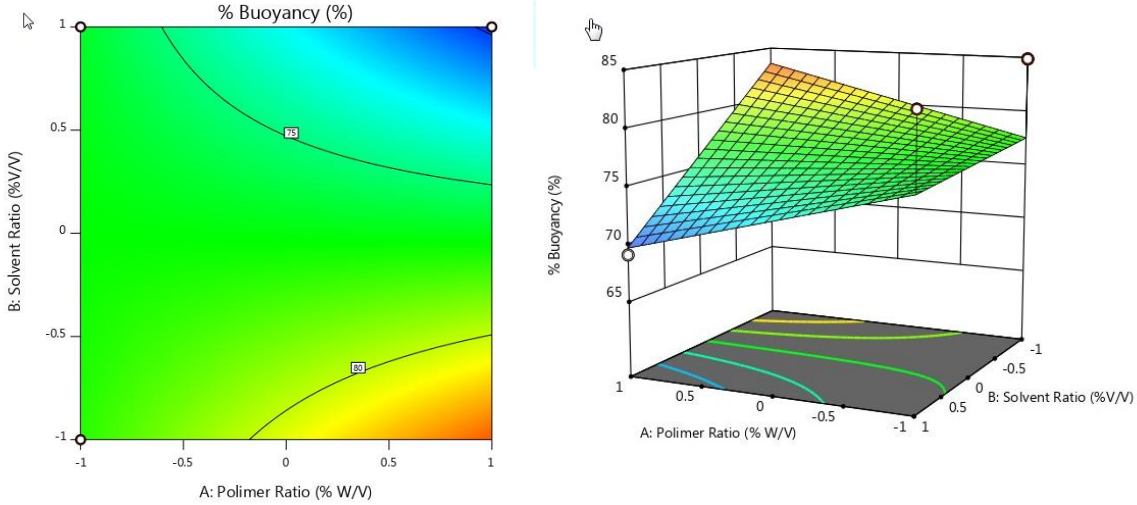

Figure 8: Contour Plot for Buoyancy after Optimization

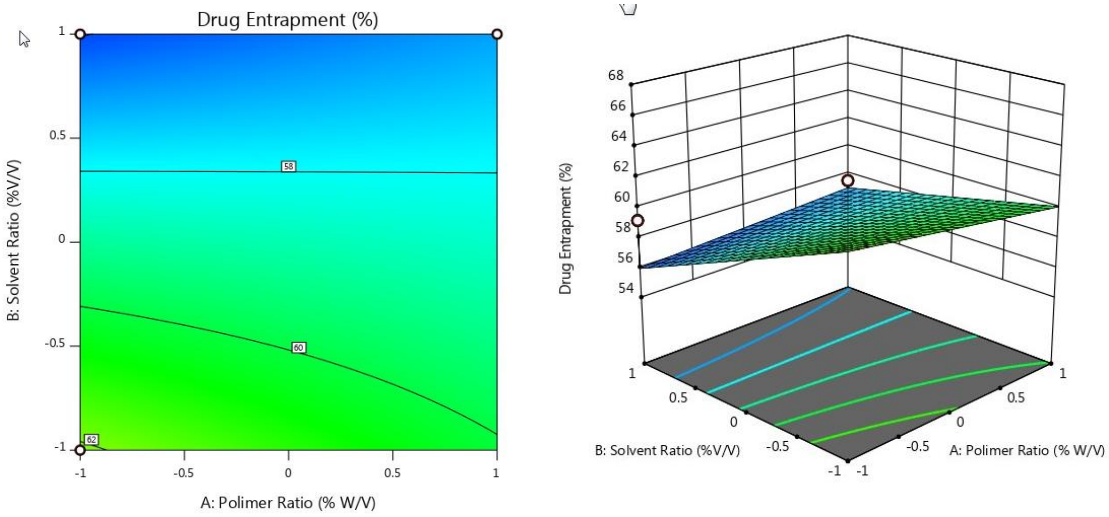

Figure 9: Contour Plot for % Drug Entrapment after Optimization

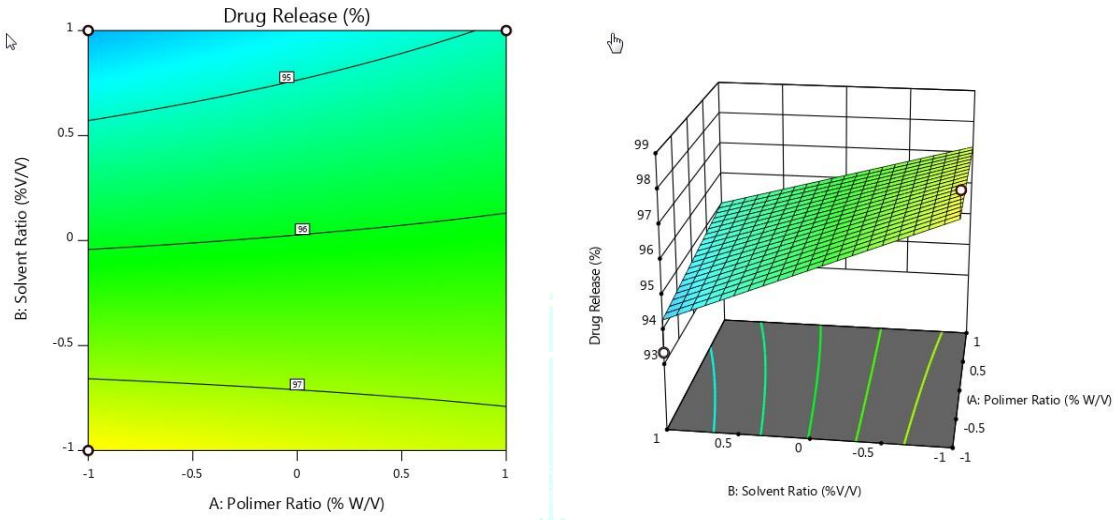

Figure 10: Contour Plot for % Drug Release after Optimization

CONCLUSION

It can be concluded that Floating Microspheres of Losartan potassium were formed by Solvent Evaporation method .The formulas LP7 of Losartan Potassium 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.

REFERENCES

1. Alaa EB, Ibrahim A, Abdulah M, Al-Mohizea. Chitosan beads of new gastroretentive system of verapamil. *Sci Pharm.* 2006; 74:175-188.
2. Bhalekar M, Avari J, Umalkar RA. Preparation and in vitro evaluation of sustained release drug delivery system for verapamil HCl. *Ind J Pharm Sci.* 2007; 69(1-3):418-22.
3. Burn S.J, Attwood D, Barnwell S.G. Assessment of a dissolution vessel designed for use with floating and erodible dosage forms. *Int. J. Pharmaceutics*. 1998; 160:213-218.
4. Guyot M, Fawaz F. Nifidifine loaded polymeric microspheres preparation and physical characteristics. Int J Pharm. 1998; 175(1): 61-74.
5. Yuvraj ST, Puspendra SN, Rani GO. Development and evaluation of floating microspheres of Verapamil HCl. Brazilian Journal of Pharmaceutical Sciences. 2007, 43(4):529-534.
6. Sato Y, Kawashima Y, Yeole PG. In-vitro evaluation of floating drug release in behavior of hallow microspheres prepared by emulsion solvent diffusion method. Eur. J Pharma & Bio Pharm. 2004; 57:235-243.
7. Sagar Balaso Sangale, *et al.* Formulation and Evaluation of Floating microspheres, International Journal of Pharma Research and development online (IJPRD) Page no.163 to 170.
8. Sameer Singh, Kalpana Prajapati, AK Pathak, A Mishra. Formulation and Evaluation of Floating Tablet of Captopril. International Journal of PharmTech Research. 3(1):333-341.
9. Lackman, L.Liberman, H.Kanig J; Theory and practice of Industrial pharmacy, II Edn, Vargase publisher, Bombay, 1976-page no 52 -57.
10. Maiti S, Dey P, Biswanath SA, Ray S. Influence of microenvironmental ph of alginate facilitated ethyl cellulose Microspheres on entrapment efficiency and release characteristics of Fluconazole. International journal of current pharmaceutical research 2010 ; 2(2):7-23.
11. Subash PCB, Srikanth RP, Ravi V, *et al.,* Formulation and evaluation of sustained release floating tablets of Diltiazem HCl using xanthine gum. Research Journal of Pharmaceutical, Biological and Chemical sciences. 2011, 2(2):319-328.
12. Shishu U, Gupta N, Agarwal N. A gastro retentive floating delivery system for 5-fluorouracil. Asian Journal of Pharmaceutical Sciences. 2007, 2(4):143-149.