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DESIGN OPTIMIZE AND EVALUATION OF FLOATING MICROSPHERES BY SOLVENT EVAPORATION TECHNIQUE OF ANTIULCER DRUG.

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ABSTRACT

Oral controlled release dosage forms have been extensively used to improve therapy of many important medications. In this we mostly focused on Gastro retentive floating microsphere containing Lafutidine, a second generation histamine H_2–receptor antagonist were prepared by solvent evaporation technique using HPMC K 15, Ethyl cellulose, EUDRAGIT® S 100, EUDRAGIT® L 100. The main objective of study to develop floating controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations. Which reduces the dosing frequency and minimized fluctuations in order to enhance the drug bioavailability. The prepared microsphere were evaluated for micromeritics study, percentage yield, in- vitro floating ability, in- vitro drug release and stability studies. The optimized formulation showed good floating for 8 hr. in vitro studies. The formulation stable at the end of 45 days with carried out by evaluated all the studies.

KEYWORD:- Microsphere, Lafutidine, EUDRAGIT® S 100, EUDRAGIT® L 100.

INTRODUCTION

Oral route is the most commonly route for drug administration and convenient used method of drug delivery but this route usually produces gastric emptying rate that varies from person to person with a short stomach transit time and the existence of large absorption window in the upper small intestine for several drugs.[1] Gastro retentive dosage forms (GRDFs) are a drug delivery formulation that are designed to be retained in the stomach for a prolonged time

and release there their active materials and thereby enabled to sustain and prolong input of the drug to the upper part of the gastrointestinal (GI) tract. Oral controlled release (CR) dosage forms (DF) have been extensively used to improve therapy of many important medications.[2] The range of techniques for the preparation of microspheres offers a variety of opportunities to control aspects of drug administration. The term ‘‘control’’ includes phenomena such as protection and masking, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. This approach facilitates accurate delivery of small quantities of potent drugs; reduced drug concentrations at sites other than the target organ or tissue; and protection of labile compounds before and after administration and prior to appearance at the site of action. The characteristics of microspheres containing drug should be correlated with the required therapeutic action and are dictated by the materials and methods employed in the manufacture of the delivery systems. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 mm. Solvent evaporation is one of the earliest methods of microsphere manufacture.[4] The polymer and drug must be soluble in an organic solvent, frequently methylene chloride. The solution containing the polymer and the drug may be dispersed in an aqueous phase to form droplets.[3] Continuous mixing and elevated temperatures may be employed to evaporate the more volatile organic solvent and leave the solid polymer–drug particles suspended in an aqueous medium. The particles are finally filtered from the suspension.

Lafutidine is newly developed second generation histamine H2–receptor antagonist, having poor water solubility and short elimination half-life up to 3.0 hours, belonging to BCS class-II drugs. It is absorbed more in the small intestine than in stomach.

MATERIAL AND METHOD

Lafutidine was procured as a gift sample from Ajanta Pharma Pvt. Ltd., Mumbai, Maharashtra. HPMC K_{15} was procured as a gift sample from ZIM Laboratories Ltd, Nagpur, Goa. Ethyl cellulose was procured from ZIM Laboratories Ltd, Nagpur. Eduragit R S 100 was procured from Evonik Pvt. Ltd, Mumbai, Eduragit R L 100 was procured from Evonik Pvt. Ltd, Mumbai. All other chemicals used were of analytical grade.

PREPARATION OF FLOATING MICROSPHERES

Microspheres were prepared using ethyl cellulose, HPMC K_{15}, HPMC K_{100}, Eduragit L100, Eduragit RS100 in variable concentration by solvent evaporation technique.[6] Drug and polymer were dissolved in methanol and dichloromethane (1:1) ratio. Internal phase was

filled in the syringe and poured in 200 ml of pH 8.0 solution containing (0.1%) tween 80 with the help of syringe, and stirred with propeller agitator at 600, 800, 1000 rpm for 60 min to allow the volatile solvent to evaporate and filtered.

ORGANOLEPTIC PROPERTIES

Microspheres were visually observed for colour and odour.

PARTICLE SIZES ANALYSIS

The dimensions of microspheres were measured with the help of digital vernier caliper (Mitutoyo CD- 6 CSX) by taking 15 microspheres from each batch. Average size of microspheres was noted.

SHAPE ANALYSIS

The shape of microspheres was determined by visual observation and radius was measured with the help of Trinocular microscope. About 5 mg microspheres were weighed microsphere taken on the glass slide, placed under microscope, radius and shape were determined with the help of taken photos by attached camera to microscope.[7]

YIELD OF MICROSPHERES (%)

Total weight of all the powdered excipients was calculated. After formulation of the microspheres weight was taken and % yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipients and drug}} \times 100$$

ENTRAPMENT EFFICIENCY (%)

The floating microspheres were weighed equivalent to 10 mg of Lafutidine and crushed. The powdered microspheres were dissolved in 0.1M HCL in volumetric flask (100ml), sonicated for 30 min and filtered through Whatmann filter paper. After suitable dilutions, the absorbance was measured at 286 nm using UV spectrophotometer, and the percentage drug entrapped was calculated.[13]

Entrapment efficiency of microspheres was calculated using the following formula:

$$\% \text{ Entrapment efficiency} = \frac{\text{The amount of drug encapsulated}}{\text{Theoretical amount of drug}} \times 100$$

% FLOATING ABILITY

The Floating ability of microspheres was determined by using a USP dissolution test apparatus II (Electrolab TD-08L) (paddle type). About 0.1g microspheres was weighed and spread over basket containing 900 ml of 0.1 M HCl. The medium was agitated with the paddle rotating at 50 rpm. Temperature was maintained at 37°C±0.5°C. After 8 hr, both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed. The percentage of floating microspheres was calculated using the following formula

$$\% \text{ Floating ability} = \frac{\text{Wt of floating microspheres}}{\text{Total mass of microspheres}} \times 100$$

DISSOLUTION STUDIES

An in-vitro dissolution study was performed for all the formulation using USP dissolution apparatus II (Electrolab TD7-08L). An accurately weighed sample of floating microspheres containing 10 mg of Lafutidine drug was placed into 900 ml of 0.1 M HCl (pH 1.2) maintained at a temperature of 37^{o}C ± 0.5^{o}C and stirred at a speed of 50 rpm at time intervals of 1 h a 10 ml aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of dissolution medium kept at 37^{o}C. The collected samples were filtered and analyzed at λ_{max} 286 nm using a UV-visible spectrophotometer against 0.1M HCl (pH 1.2) taken as a blank.[14]

FORMULATIONS OF FLOATING MICROSPHERES OF LAFUTIDINE

Batch No.	Composition										
	Drug (g)	EC (g)	HPMC K_{15} (g)	HPMC K_{100} (g)	Eduragit L100 (g)	Eduragit RS 100 (g)	DCM (ml)	Ethanol (ml)	Sol. (pH 8.0) ml	Tween 80(0.1 % v/v) ml	rpm
PL1	0.03	3.00	0.25	------	-------	------	10	10	200	0.2	600
PL2	0.03	2.50	0.50	-------	-------	------	10	10	200	0.2	800
PL3	0.03	2.00	1.00	------	------	------	10	10	200	0.2	1000
PL4	0.03	3.00	------	0.25	------	------	10	10	200	0.2	600
PL5	0.03	2.50	------	0.50	------	------	10	10	200	0.2	800
PL6	0.03	2.00	------	1.00	------	------	10	10	200	0.2	1000
PL7	0.03	3.00	------	------	0.25	------	10	10	200	0.2	600
PL8	0.03	2.50	------	------	0.50	------	10	10	200	0.2	800
PL9	0.03	2.00	------	------	1.00	------	10	10	200	0.2	1000
PL10	0.03	3.00	------	------	------	0.25	10	10	200	0.2	600
PL11	0.03	2.50	------	------	------	0.50	10	10	200	0.2	800
PL12	0.03	2.00	------	------	------	1.00	10	10	200	0.2	1000

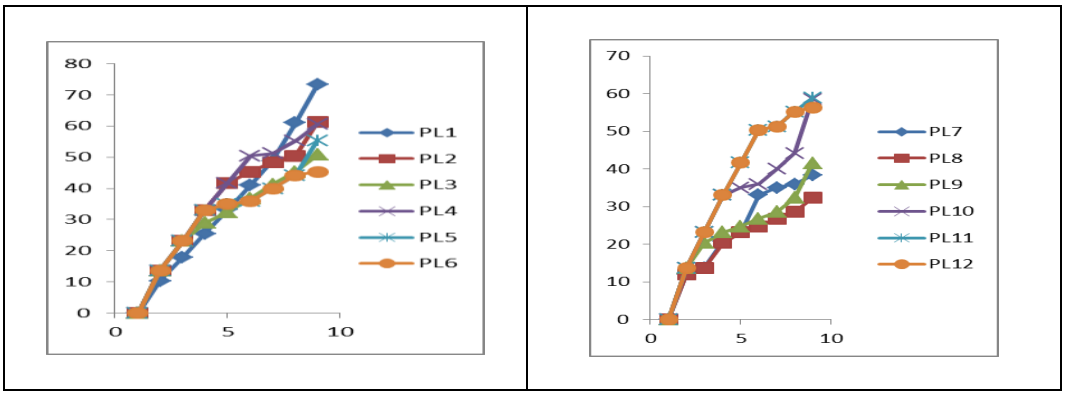
EVALUATION PARAMETER OF PRELIMINARY BATCH

Batch No.	Parameter					
	Size (µm)	Shape	Yield (%)	Entrapped efficiency (%)	Drug release (%)	Floating ability (%)
PL1	200-250	spherical	67.60	77.20	73.20	70.50
PL2	250-300	spherical	48.60	63.70	61.20	65.50
PL3	250-350	spherical	42.60	62.80	50.80	60.12
PL4	400-550	spherical	65.50	65.60	60.57	62.20
PL5	500-650	spherical	43.03	53.50	55.30	58.50
PL6	350-450	spherical	21.63	45.60	45.30	55.60
PL7	800-900	spherical	68.73	42.90	41.60	52.20
PL8	600-800	spherical	34.49	42.60	32.30	50.50
PL9	800-900	spherical	21.20	35.80	38.30	48.20
PL10	750-900	spherical	37.01	60.20	58.90	59.60
PL11	600-700	spherical	32.30	58.30	58.60	56.10
PL12	500-650	spherical	25.20	48.50	56.30	48.20

CUMULATIVE PERCENT DRUG RELEASE

Batch No.	Time (hr)								
	0	1	2	3	4	5	6	7	8
PL1	0	10.32	17.87	25.5	33.22	41.02	48.09	61.00	73.20
PL2	0	13.64	23.17	33.06	41.69	45.32	48.42	50.4	61.20
PL3	0	13.64	23.17	28.09	32.40	36.82	41.25	45.35	50.8
PL4	0	13.64	23.17	33.06	41.69	50.4	51.26	55.23	60.57
PL5	0	13.64	23.17	33.06	35.00	36.00	40.00	44.20	55.30
PL6	0	13.64	23.17	33.06	35.00	36.00	40.00	44.20	45.30
PL7	0	13.64	20.37	23.17	24.72	26.82	28.63	32.30	41.60
PL8	0	11.98	13.64	20.37	23.17	33.66	35.00	36.00	38.30
PL9	0	11.98	13.64	20.37	23.17	24.72	26.82	28.63	32.30
PL10	0	13.64	23.17	33.06	41.69	50.40	51.26	55.23	58.90
PL11	0	13.64	23.17	33.06	35.00	36.00	40.00	44.20	58.60
PL12	0	13.64	23.17	33.06	41.69	50.40	51.26	55.23	56.33

% CUMULATIVE DRUG RELEASE OF PRELIMINARY BATCH



DESIGN OF EXPERIMENTS

Factorial design was applied to design the experiments. On the basis of Preliminary trials concentration of EC, HPMC K_{15} and stirring speed were used as independent variables. Whereas %yield, mean microsphere size, %Entrapment efficacy, %Floating capacity and %drug release after 8hr, were kept as dependent variables.[16] Formulations L1 to L9 were prepared using EC and HPMC K_{15} concentration at three different levels.

INDICATE VARIABLES

Independent variables	Dependent variables
X_1= ethyl cellulose	Y_1= % entrapment efficiency
X_2=HPMC K 15	Y_2= % floating ability
	Y_3= % Drug release (after 8 hr)

FACTORS AND LEVELS WITH THEIR REAL VALUES

Factors	Low level (-1)	Middle level (0)	High level (1)
Ethyl cellulose %	11 %	13 %	15%
HPMC K15 (g)	0.500	1.000	1.500

FORMULATIONS OF OPTIMIZED BATCH MICROSPHERES OF LAFUTIDINE

Batch No.	Composition							
	Drug (g)	EC (g)	HPMC K_{15} (g)	DCM (ml)	Ethanol (ml)	Sol. (pH 8.0) (ml)	Tween80 (0.1 % w/w)	rpm
L1	0.03	3.0	1.0	10	10	200	0.1	800
L2	0.03	3.0	1.5	10	10	200	0.1	800
L3	0.03	2.6	1.5	10	10	200	0.1	800
L4	0.03	3.0	0.5	10	10	200	0.1	800
L5	0.03	2.2	1.5	10	10	200	0.1	800
L6	0.03	2.2	0.5	10	10	200	0.1	800
L7	0.03	2.6	1.0	10	10	200	0.1	800
L8	0.03	2.6	0.5	10	10	200	0.1	800
L9	0.03	2.2	1.0	10	10	200	0.1	800

RESULT OF OPTIMIZED BATCHES OF LAFUTIDINE LOADED MICROSPHERES WITH FACTORS (LEVELS INCLUDING CODED VALUES)

Std	Run	Factor 1 Conc. of E.C. %	Factor 2 Conc. of HPMC K_{15} %	Response 1 Entrapment efficiency %	Response 2 Floating ability %	Response 3 Drug release %
6	1	1.00	0.00	89.90±1.53	80.23±2.01	86.3±0.63
9	2	1.00	1.00	92.33±1.22	81.20±2.62	76.30±1.60
8	3	0.00	1.00	78.62±2.01	78.42±0.73	75.50±0.96
3	4	1.00	-1.00	88.65±1.99	76.80±1.98	92.40±0.95
7	5	-1.00	1.00	68.40±2.29	72.50±1.99	71.32±0.64
1	6	-1.00	-1.00	66.80±2.21	74.30±0.98	88.4±0.78

5	7	0.00	0.00	77.68±1.99	76.82±1.00	85.82±0.96
2	8	0.00	-1.00	76.50±1.81	74.30±1.01	90.80±0.86
4	9	-1.00	0.00	70.20±1.79	72.50±2.01	84.30±1.92

RESULTOF OPTIMIZED BATCHES OF LAFUTIDINE LOADED MICROSPHERES

Batch No.	Parameter					
	Size (µm)	Shape	Yield (%)	Entrapped efficiency (%)	Floating ability (%)	Drug release %
L1	100-200	spherical	58.60	89.90±1.5	80.23±2.01	86.3±0.63
L2	100-200	spherical	69.73	92.33±1.2	81.20±2.62	76.30±1.60
L3	100-200	spherical	81.60	78.62±2.0	78.42±0.73	75.50±0.96
L4	100-200	spherical	84.66	88.65±1.9	76.80±1.98	92.40±0.95
L5	350-450	spherical	86.40	68.40±2.29	72.50±1.99	71.32±0.64
L6	350-450	spherical	65.50	66.80±2.2	74.30±0.98	88.4±0.78
L7	100-200	spherical	68.73	77.68±1.9	76.82±1.00	85.82±0.96
L8	100-200	spherical	89.30	76.50±1.8	74.30±1.01	90.80±0.86
L9	200-400	spherical	84.66	85.45±1.79	72.50±2.01	84.30±1.92

CUMULATIVE PERCENT DRUG RELEASE

Batch No.	Time (hr)								
	0	1	2	3	4	5	6	7	8
L1	0	4.91± 0.63	14.47 ±1.2	23.72 ±1.6	33.9 ±2.6	44.19 ± 0.6	53.76 ±0.98	77.76±1. 6	86.3 ± 0.63
L2	0	12.76 ±1.6	17.03 ±1.62	13.64 ± 1.62	34.01 ±0.64	47.6 ± 2.67	59.69 ±0.64	69.07 ±2.67	76.3 ± 1.60
L3	0	4.91 ± 1.65	13.64 ± 1.62	22.47 ± 0.98	31.87 ± 1.69	41.25 ± 0.64	50.79 ± 1.28	60.84 ± 0.64	75.50 ± 0.96
L4	0	4.09 ± 2.67	12.81 ± 0.86	21.63 ± 1.69	30.54 ± 0.86	39.55 ± 2.01	48.25 ± 0.64	57.45 ± 1.69	71.32 ± 0.95
L5	0	10.32 ± 2.01	17.87 ± 0.64	25.5 ± 0.98	32.81 ± 1.28	40.6 ± 1.62	48.48 ± 1.69	54.47 ± 1.62	60.57 ± 0.64
L6	0	10.73 ± 1.28	18.7 ± 0.98	26.76 ± 2.67	34.9 ± 0.64	43.14 ± 0.64	51.45 ± 1.62	59.86 ± 1.28	88.4 ± 0.78
L7	0	11.98 ± 1.69	20.37 ± 0.64	28.86 ± 1.65	37.86 ± 2.01	46.53 ± 2.67	55.71 ± 1.65	59.86 ± 1.28	88.4 ± 0.96
L8	0	10.32 ±1.69	17.87 ±0.86	25.5 ± 2.01	33.22 ± 0.64	41.02± 0.64	48.9 ± 0.64	61 ± 1.65	90.8 ± 0.86
L9	0	13.64 ± 2.01	23.17 ± 1.28	33.06 ± 0.64	41.69 ± 1.69	50.4 ± 1.28	63.34± 0.64	73.94 ± 1.28	84.3 ± 1.92

SIGNIFICANT SUMMARY FOR ANOVA FOR THE RESPONSE PARAMETER

Source	Sum of squares	d. f.	Mean square	F- value	p- value probe > F
R 1 (%)	**Entrapment efficiency**				
Model	723.73	2	361.87	177.14	<0.0001(S)
X_1	714.61	1	714.61	349.81	<0.0001(S)
X_2	9.13	1	9.13	4.47	0.0790(NS)
X_1 X_2	735.99	6	2.04		

R 2 (%)	Floating ability				
Model	76.86	3	25.62	28.63	0.0014(S)
X_1	59.72	1	59.72	66.75	0.0004(S)
X_2	7.53	1	7.53	8.41	0.0338(S)
X_1 X_2	9.61	1	9.61	10.74	0.0220(S)
X_1^2	4.47	5	0.89		
X_2^2	8133	8			
R 3 (%)	**Drug release**				
Model	431.81	5	86.36	94.42	0.0017(S)
X_1	20.09	1	20.09	21.97	0.0184(S)
X_2	391.72	1	391.72	428.28	0.0002(S)
X_1 X_2	0.24	1	0.24	0.26	0.6437(NS)
X_1^2	1.51	1	1.51	1.66	0.2886(S)
X_2^2	18.24	1	18.24	19.94	0.0209(S)
$X_1^2X_2^2$	434.55	8			

EVALUATION OF DEPENDENT VARIABLES AND MATHEMATICALLY MODELING

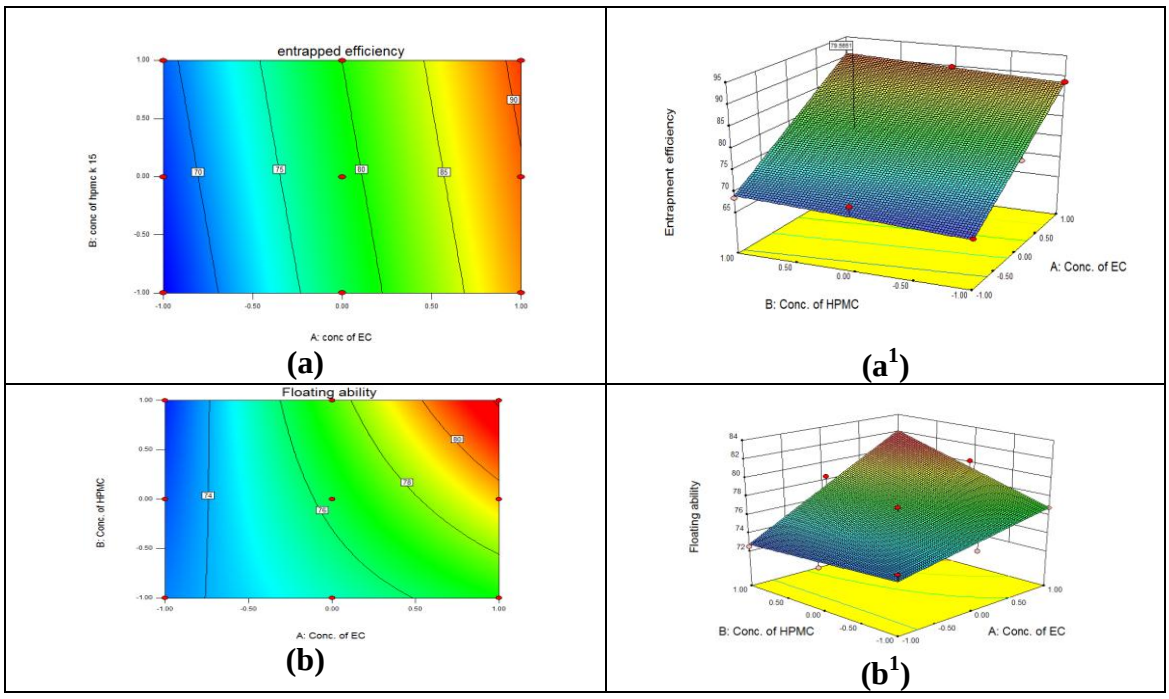
Mathematically relationship generated using MLRA for the studied response variables are expressed in equation 1 to 3.

% Entrapment efficiency (Y_1) = $78.78+10.91 X_1+10.79 X_2-+1.23X_1X_2$ …… 1

% Floating ability (Y2) = $76.34+3.15 X_1+1.12 X_2+1.550 X_1X_2$ …… 2

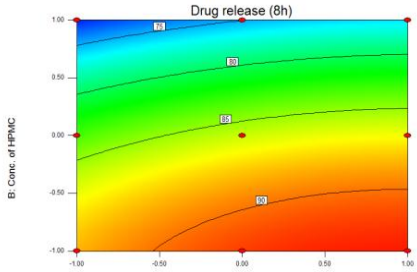
% Drug release (Y3) = $86.05+1.83X_1-8.08X_2+0.245 X_1X_2-0.87X_1^2-3.020 X_2^2$ ….. 3

These effects can be further explained by response plots and contour plots generated using equation 1, 2 and 3.



(a) **(a^1)**

(b) **(b^1)**



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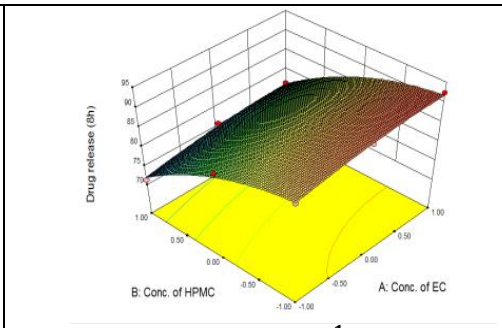


(c^1)

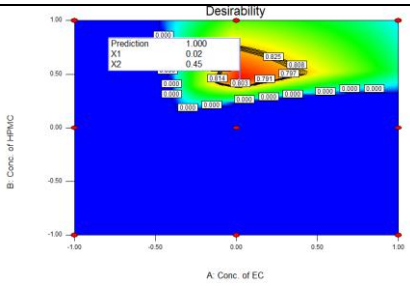
SEARCH FOR OPTIMUM FORMULATION OF LAFUTIDINE LOADED MICROSPHERES

The results for the feasibility to find the suitable region for further location of optimum formulation are presented in table 7.13 the criteria for selection of suitable feasible region was primarily based upon the value of % entrapment efficiency,% floating ability, % drug release. One formulation was selected on the basis of the following criteria.

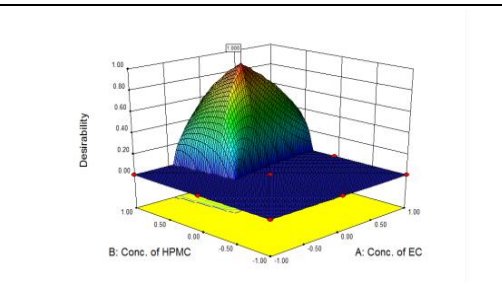
CRITERIA FOR FORMULATION

Sr.No.	Response	Region
1	% Entrapment efficiency	65-92.33%
2	% Floating ability	70-81.20%
3	% Drug release	70-92.40%

DESIRABILITY AND OVERLAY PLOT FOR SEARCHING OPTIMUM FORMULATION OF LAFUTIDINE LOADED MICROSPHERES



(a)



(b)

Sr.No.	Factor	Optimized ratio	Calculated quantity
1	X_1	0.02	2.700 g (13.50%)
2	X_2	0.45	0.450 g (2.25%)

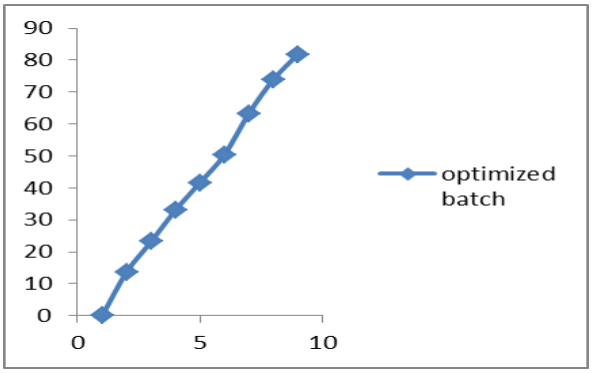
RESULT OF EXPERIMENTS FOR CONFORMING OPTIMIZATION CAPABILITY

Batch	Composition (coded value)		Response	Predicted value	Actual value	% error
	X_1	X_2				
Optimized batch	0.02	0.45	% entrapment efficiency	79.56	79.71±0.27	0.31
			% floating ability	76.92	81.25±0.13	0.071
			% Drug release (after 8 hr)	81.85	82.08±0.36	0.33

CUMULATIVE PERCENT DRUG RELEASE FROM OPTIMIZED BATCH

Time (h).	% Drug release
0	0
1	13.64±0.78
2	23.17±0.64
3	33.06±1.24
4	41.69±1.68
5	50.4±1.28
6	63.34±0.64
7	73.94±0.84
8	81.85±0.36

CUMULATIVE PERCENT DRUG RELEASE



STABILITY STUDIES

Stability studies of the optimized formulation were carried out to know

1. Whether the chemical change or degradation of the active ingredient has occurred this may lower the therapeutic potency of active ingredient over storage period.
2. Whether any toxic degradation product has formed which may be undesirable.

In any rational design and evaluation of dosage form for drugs, the stability of the active ingredient must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity however the studies will take a longer time and hence it would be convenient to carry out

the accelerated stability studies where the product is stored under extreme conditions of temperature and humidity.

To assess the drug and formulation stability, stability studies were done according to ICH guidelines. Optimized formulation sealed in aluminum packaging coated inside with polyethylene and various replicates were kept in the environmental chamber (Bio-technics India Ltd.) maintained at 40^{o}C and 75%Rh for 45 days. At the end of studies, samples were analyzed for the drug entrapment % ,drug released study and floating ability.

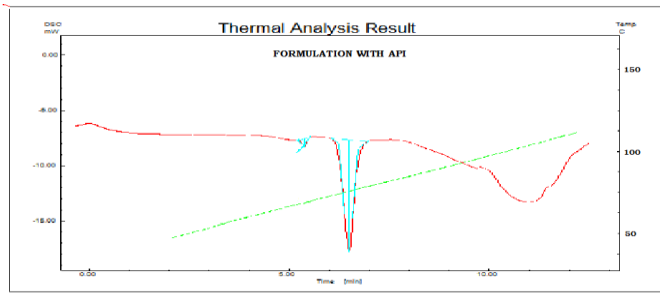
DAYS	% entrapment efficiency	%Drug release (after 8 h)	% floating ability
0	79.71	82.08	<8
15	79.09±0.70	81.17±0.37	<8
30	79.49±0.71	81.60±0.64	<8
45	79.65±0.71	81.88±0.98	<8

STABILITY DATA OF OPTIMIZED FORMULATION

The stability studies were carried out on optimized formulation. The formulation was stored at 40^{o}C±2^{o}C/75±5%Rh (climatic zone of IV condition for accelerating testing) for 45 days to assess its stability. After 15, 30 and 45 days samples withdrawn and retested for physical appearance, %drug entrapment and % drug release and floating studies as shown in table 7.19 and the result indicated that the formulation was able to retain its stability for 45 days.

INFRARED SPECTRUM OF LAFUTIDINE MICROSPHERES

DSC OF LAFUTIDINE MICROSPHERES



DISCUSSION

Ulcer is a major cause of death in India. Lafutidine has a local action in stomach as it is used in the treatment of gastric ulcers, duodenal ulcers and gastric mucosal lesions associated with acute gastritis and acute exacerbation of chronic gastritis. Lafutidine primarily absorbed from upper part of gastrointestinal tract. The main objective of this study was to develop gastro retentive controlled release drug delivery of Lafutidine that can provide constant plasma drug level for longer duration, thereby reducing the dose frequency, increase in drug bioavailability, minimizing fluctuation in plasma drug concentration and increased patient compliance.

Appearance, melting points, loss on drying, λ_{max}, IR study and DSC study of drug Lafutidine were carryout as per the specification of J.P. It was observed that the obtained sample of lafutidine complies with the standard of quality mentioned in J.P. Standard calibration curve of Lafutidine (absorbance Vs concentration) was found to be linear and obeyed Beer Lambert's law in the range of 0-25µg/ml. EC and HPMC K $_{15}$ were evaluated for their standard. It was observed that they complies with the standard of quality as per prescribe official books.

Preliminary batches of Lafutidine floating microspheres were prepared by solvent evaporation technique using ethylcellulose as floating polymer and HPMC K_{15}, HPMC K_{100}, Eduragit L100 and Eduragit RS100 as controlled release polymer in various concentrations. From the results of preliminary batches, it was observed that polymer concentration is important parameter in the formulation of floating microspheres.

As the EC concentration was decreased from 15 % to 10% (PL1-PL12), and concentration of HPMC K_{15} (PL1-PL3), HPMC K_{100} (PL3-PL6), Eduragit L100 (PL7-PL9), Eduragit R S100 (PL10-PL12) were increased from 2.5% to 7.5%; the % yield, % entrapped efficiency, % floating ability, % drug release from microspheres were decreased. It was observed that when the concentration of ethylcellulose decreases in internal phase and drop of internal phase comes in contact with external phase, it breaks. Agglomeration of polymer around shear shaft and breaking of injected drop of internal phase was observed, this may be due to increased in concentration of HPMC K_{15} HPMC K_{100}, Eduragit L100 and Eduragit R S100. The % yield of microspheres was decreased with increase in stirring speed from 600 to 1000 rpm (Table No.7.7), this may be due to at high stirring speed polymers aggregated around the propeller shaft and the resultant yield of microsphere was less. It was also observed that as the stirring

speed was increased, the size of microspheres was decreased to some extent. This may be due to stronger shear forces and increased turbulences.

Improvement in formulation and development was carried out by optimization technique with the help of factorial design. Factorial design was applied to design the experiments. On the basis Preliminary trials, concentration of EC, HPMC K_{15} and stirring speed were used as independent variables. Where as % yield, mean microsphere size, % entrapment efficacy, % floating capacity and % drug release after 8h, were kept as dependent variables. Formulations L1 to L9 were prepared using EC and HPMC K_{15} concentration at three different levels (table No. 7.11).

From the evaluation study, it was observed that, as the concentration of EC was increased, more uniform spherical microspheres were observed. When the concentration of HPMC K_{15} was decreased and ethylcellulose concentration was increased, the % yield of microspheres was increased (58.60-89.30%). At medium level of ethylcellulose (13%), and low level of HPMC K_{15} (2.5%) (Batch L8), the % yield of microspheres was at maximum (89.30%).

At high level of HPMC K_{15} (7.5%) and high level of EC (15%) (batchL2), floating ability and % entrapment efficiency were increased because the drug was immersed properly in evaporating solvent with the polymer. When concentration of both polymers was kept at low level (Batch L9), then the % floating ability and % entrapment efficiency were decreased. At low level of HPMC K_{15} (2.5%) and high level of EC (15%)(batch L4), drug release was maximum at 8 hr (92.40%)(Table7.12).

The formulation was further optimized using design expert software by feeding predicted values for responses like entrapment efficiency (R1) to 79.56, % floating ability (R2) to 76.92, and % drug release (R3) to 81.85, and actual values were generated for responses [R1, R2, R3 (79.71, 81.25, 82.08)] for ethyl cellulose (XI) and HPMC K15 (X2) to 13.50% and 2.25% respectively for confirming capability of optimized batch.

From DSC study, it was observed that there was no interaction between drug lafutidine, and polymers EC and HPMC K_{15}, so optimized batch was formulated in capsule dosage form. Lafutidine microspheres loaded capsules were evaluated for weight variation test, disintegration test and % cumulative drug release as per the specification of I.P. It was

observed that, the lafutidine microspheres loaded capsule were given cumulative drug release in controlled manner in comparision to marketed preparation i.e. tablets.

CONCLUSION

Gastroretentive drug delivery system of Lafutidine floating microspheres were successfully developed using solvent evaporation method with the help of 3^2 factorial designs. Concentration of ethylcellulose 13.50% and concentration of HPMC K_{15} 2.25 % was taken then resultant microspheres was given controlled manner drug release (82.08±0.36) in 8 h. The *in-vitro* results indicated that the microspheres were potentially useful. The solvent evaporation method was found to be simple, reproducible, easily controllable, economical, and consistent process. Additionally, the excipients used for the formulation of this buoyant system were cheap and easily available. Other drugs for the use in gastro retentive delivery can be incorporated in this multiple- unit buoyant system. Therefore, these types of multiple-unit buoyant microspheres can be commercially processed easily and potentially better than other marketed formulation i.e. tablets.

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