Research paper

“Development of Novel Multicomponent Floating Tablet Formulation of Lafutidine and Domperidone: Design and Characterization.”

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Abstract

Lafutidine and domperidone are H2 blocker and antiemetic activity respectively, to improve their retention time and bioavailability floating drug delivery system method was used. This appears to be a promising approach for enhancing the bioavailability of pharmaceutical compounds. The purpose of this study was to prepare, evaluate Floating tablet of lafutidine-domperidone by direct compression method. Their characterization involved melting point, solubility, Fourier Transform Infrared Spectroscopy (FTIR), and Differential Scanning Calorimetry (DSC). The tablet formulation was optimizes using 32 factorial designs. In which concentration of HPMC K 100 and sodium bicarbonate were selected as independent variables, where as the % of drug release and Total floating tablet as dependent variables. F7 batch was selected as an optimized, used for *in- vivo* bioavailability study. According to micromeritic analysis of tablet formulation shows good flowability. Post compression of tablet analysis shows good results according to IP. The in-vitro drug release of all formulation was found to be 81.96 - 86.28% for domperidone and lafutidine. *In-vivo study* of floating tablet shows significant result as compare to marketed formulation. The floating tablet dosage form of lafutidine-domperidone was successfully prepared, evaluated and to improve its bioavailability.

Keywords: Lafutidine, domperidone, total lag time, bioavailability.

1.Introduction

Peptic ulcer disease is major medical issue. In India, the lifetime incidence of peptic ulcer was 11.22 percent, with a point prevalence of 4.72 percent. Peptic ulcers are acid induced lesions that damage the stomach and duodenum .They can be identified by damaged mucosa that has defects which has defects which has defects which has extended to the muscularis propria or submucosa .An imbalance between aggressive elements and the gastro duodenal mucosa capacity to defend and cure itself leads to ulcers. Peptic ulcer disease is often defined as a mucosal break greater than 3-5 mm in the stomach or duodenum with a visible depth. An endoscopic diagnosis involves visual examination with an endoscope, while dyspepsia is diagnosed based on symptoms alone, such as epigastric pain, retrosternal pain, early satiety, nausea, bloating, belching, or postprandial distress.Endoscopically confirmed peptic ulcers without H pylori infection are treated with a PPI until healed, along with elimination of any other known risk factors Patients testing positive for H pylori should receive eradication therapy. The choice of antibiotics is determined by antibiotic resistance patterns Medication related peptic ulcer disease A COX 2-selective NSAID in combination with a PPI may be preferred in these patients Histamine 2 receptor antagonists are effective in preventing duodenal ulcers among NSAID users at high doses of famotidine (80 g daily) prevent gastric ulcers3Gastroesophageal reflux disease (GERD) is a very common disorder with increasing prevalence. It is estimated that 20%-25% of Americans experience GERD symptoms weekly.

Excessive reflux of acidic often with alkaline bile salt gastric and duodenal contents results in a multitude of symptoms for the patient including heartburn, regurgitation, cough, and dysphagia.The ulcer preventive and the H2 receptor blocking activity of lafutidine have been demonstrated in numerous antiulcer pre-clinical trials.. Lafutidine produce gastroprotective effect which is related to its antisecretory activity and ability to activate a sensory neuron-dependent mechanism for the defence. It has been reported to increased action on the gastric mucosal defensive capacity and enhancement of mucosal blood flow via capsaicin-sensitive sensory neurons there by providing gastro protective effects against necrotizing agents like nonsteriodal anti-inflammatory drugs. Domperidone, a peripheral dopamine receptor antagonist, can directly act on the gastric wall and increase lower oesophageal sphincter pressure, thereby slowing down or preventing the backing up of gastric contents into the oesophagus, and reducing the incidence of acid reflux . Domperidone is also a gastroprokinetic agent. It can treat dyspepsia caused by gastro oesophageal reflux, by facilitating gastric emptying, and preventing the reflux of gastric contents Solid oral dosage forms like capsules and tablets provide specific drug concentrations in the bloodstream but lack control over the drug delivery system, leading to major fluctuations in plasma drug concentrations. The most convenient and preferred method for drug delivery to the systemic circulation is oral

administration. To enhance therapeutic outcomes, oral controlled-release drug delivery systems are employed, ensuring a consistent drug concentration in the bloodstream and reducing side effects. Oral administration is the most convenient and preferred method for drug delivery due to ease of dosing, patient compliance, and flexibility in drug formulation. Floating Drug Delivery Systems (FDDS) are gastro-retentive dosage forms designed to extend gastric residency time. These considerations have led to the development of oral controlled-release (CR) dosage forms with gastric retention capabilities, which help control the location of the drug delivery system., especially for drugs exhibiting an absorption window in the GI tract or drug with a stability problem, in a specific region of the GI tract offers several advantages.

2.Material and method

2.1 Material

Lafutidine and domperidone procured from Yarrow chemicals and Dhamtac chemicals respectively. While HPMC K 100 ,HPMC K 15,Lactose ,sodium bicarbonate procured from Unique chemicals, Kolhapur.

2.2.Methodology

2.2.1.Compatiblity study

2.2.1.1Fourier transform infrared Spectroscopy (FTIR)

In development of formulation drug and Excipients are in close contact with each other and stability of developed formulations depends on these interactions. Proper care was taken while selecting the suitable Excipients for formulations. Drug sample or Excipients sample mixed with potassium bromide and FTIR spectra was taken. The spectrum of drug was compared with combined spectra of Excipients and drug. Shifting or disappearance of drug peak was studied.

2.2.1.2. Differential Scanning Calorimetry (DSC)

A Differential Scanning Calorimetry was used to perform DSC on pure drug and Excipients. Approximately 5 mg sample was weight and place into aluminum pan for examine. They were scanned under nitrogen gas flow

2.2.2 Design of experiment

A two factor ,3 level (32)factorial design for floating tablet of lafutidine-domperidone was used for optimization of the floating tablet of lafutidine-domperidone formulation where the two factors were evaluated each at three different levels (low, medium, high) and experimental trials were

performed using all possible nine combinations using the software : Design Expert software (Version 7.0.0, Stat-Ease Inc., USA).The independent variables chosen for floating tablet of lafutidine – domperidone were the Hydroxypropyl methylcellulose (X1) and Sodium Bicarbonate (X2). Whereas drug release (Y1), and total floating time (Y2) were selected as dependent variable. Amount of lafutidine and domperidone were kept constant (10 mg and 30 mg Equivalent respectively) in all batches for the preparation of floating tablet. The independent and dependent variables in 32 factorial design approach for formulation of floating tablet.

Table no.1.Design of Experiment

Factors	**Level used, actual (coded)**		
	Low (-1)	Medium (0)	High (+1)
Independent variables			
Factor 1 (X1) (HPMC K 100)	40	60	80
Factor 2 (X2) (Sodium bicarbonate)	30	40	50
Dependent variables			
Drug Release (Y1)	Minimize		
Total Floating time (Y2)	Maximize		

2.2.3.Formulation

Floating tablet of Lafutidine and domperidone was formulated by direct compression method.

Table no.2.Formulation of Floating tablet

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Lafutidine	10	10	10	10	10	10	10	10	10
Domperidone	30	30	30	30	30	30	30	30	30
HPMC K 100	40	60	80	40	60	80	40	60	80
Sodium Bicarbonate	30	30	30	40	40	40	50	50	50
HPMC K 15	45	45	45	45	45	45	45	45	45
MCC	50	50	50	50	50	50	50	50	50
Lactose	100	80	60	90	70	50	80	60	40
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2

2.2.4.Evaluation of Floating tablet

2.2.4.1. Hardness -The hardness of the 5 tablet was determined by using Monsanto hardness tester. And expressed in Kg / cm^2.

2.2.4.2. Weight Variation-Randomly 20 tablets were weighted individually to check weight variation. According to IP limit for weight variation is 80-250 mg ± 7.5% and more than 250 mg ± 5%.

2.2.4.3.Thickness - The thickness of 05 the tablets was measured by Vanier calliper.

2.2.4.4. Friability- Friability of the tablets was determined by using Roche friability tester. The chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. A 6.5 gram sample of tablets was placed in a friabilator rotating at 25 rpm, dropping tablets 6 inches each revolution for 100 revolutions. Tablets were dedusted with a muslin cloth and reweighed.

$F = (1- W / W1) \times 100$

Where, W is the weight of the tablets before the test and W1 is the weight of the tablet after the test.

2.2.4.5.Drug content- The drug content was carried out by weighing 10 tablets and their average weight was calculated. These tablets were triturated to get fine powder. The weighed powder equivalent to 100 mg of Lafutidine and domperidone , dissolved in a 100 ml volumetric flask containing 50 ml of 0.1 N HCL and volume was made up to 100 ml with same solvent. The volumetric flask was shaken using sonicator for 1 hr. and after suitable dilution with HCl the drug content was determined using UV- spectrophotometer at 289nm and 286 nm respectively.

2.2.4.6.Buoyancy lag time and Total floating time- The *in vitro* buoyancy was determined by the floating lag time. The tablets were placed in100 ml beaker containing 0.1N HCl. The floating lag time was determined as the time required for the tablet to rise to the surface. The floating duration of all tablets was then measured.

2.2.4.7.*In vitro* Dissolution Study- *In vitro* drug release studies for the prepared floating tablets were conducted for a period of 12 hours using USP XXIV type-II (Paddle) dissolution test apparatus (Electro lab, Mumbai.) at 37□0.5ºC and 75 rpm speed using 900 ml of 0.1N HCL as dissolution medium. At predetermined intervals, 5 ml samples were withdrawn from the dissolution medium and replaced with fresh medium to maintain sink conditions.After filtration and appropriate

dilution, the samples were analyzed for Lafutidine and Domperidone by UV spectrophotometer at 314 nm. The amount of drug present in the samples was calculated.

3.Result and Discussion

3.1.Identification of Drugs

3.1.1.Melting point-Melting point of Lafutidine and Domperidone was found to be 98.32^{0}C and 247.89^{0}C respectively.

3.1.2.Spectroscopic analysis-λmax value for Lafutidine and Domperidone by Spectrophotometric method was found to be 289 nm and 286 nm respectively.

3.1.3. Fourier Transform Infrared Spectroscopy (FTIR) The IR spectral analysis identifies the characteristic functions present in substances. To identify a given drug sample, Fourier Transform Infrared Spectroscopy (FTIR) spectra of the sample were recorded and compared with standard reference spectra from the literature. FTIR analysis was conducted on the obtained samples of Lafutidine and Domperidone. Comparison of their FTIR peaks with standard references confirmed the samples as Lafutidine and Domperidone.

3.1.4. Differential scanning calorimetry (DSC)- Differential scanning calorimetry (DSC) gives information about transition temperature. The DSC technique provides qualitative physicochemical status of drug which is reported in endothermic or exothermic process.

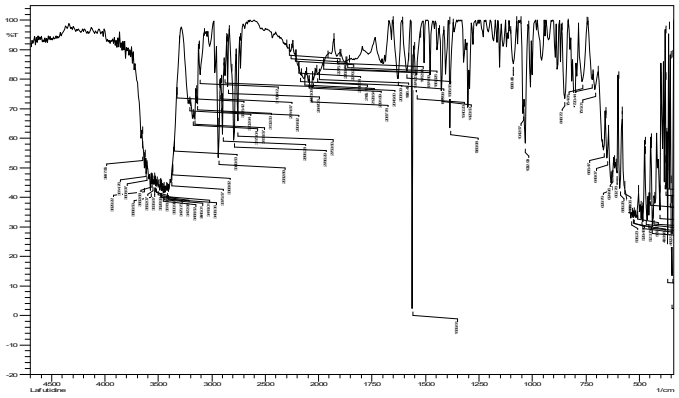


Fig. no.1. FTIR Spectra of lafutidine

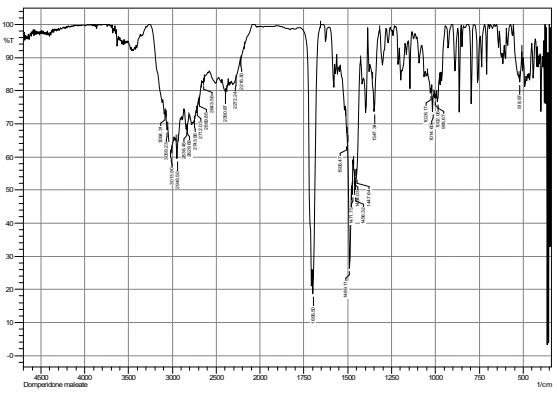


Fig. no.2. FTIR Spectra of Domperidone

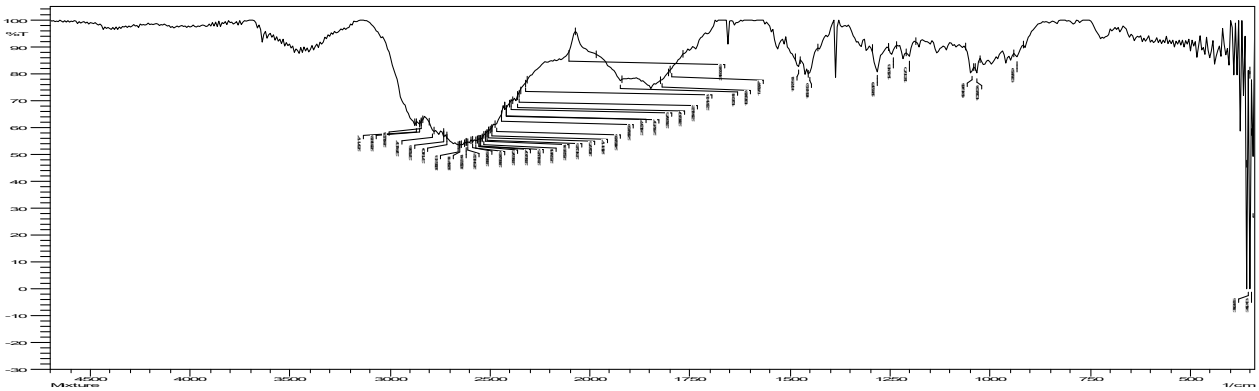


Fig. no.3. FTIR Spectra of Physical Mixture

3.2. Evaluation of Floating Tablet

Table no.3. Evaluation of Floating Tablet

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation(mg)	309	310	310	308	311	310	308	311	310
Hardness (kg/cm^2)	5.3	6.8	4.8	4.6	5.8	4.1	5.3	6.1	4.9
Thickness(mm)	4.0	3.96	3.9	4.03	4.1	4	4.06	3.9	4
% Friability	0.5	0.12	0.54	0.10	0.23	0.23	0.12	0.2	0.12
Tensile strength	1.4	1.53	1.89	1.78	1.30	1.70	1.85	1.56	1.93
Disintegration time(min)	>30	>30	>30	>30	>30	>30	>30	>30	>30

3.3. Buoyancy Floating lag time and Total floating time

Table no.4. Buoyancy Floating lag time and Total floating time

Batches	Total Floating Time	Floating Lag Time
F1	13 hr	55.3 sec
F2	12hr	1 min 23 sec
F3	12 hr	1 min 27 sec
F4	14 hr	44.2 sec
F5	13hr	33.12 sec
F6	15 hr	30.75 sec
F7	15 hr	27 sec
F8	14 hr	30.17 sec
F9	12 hr	39.67 sec

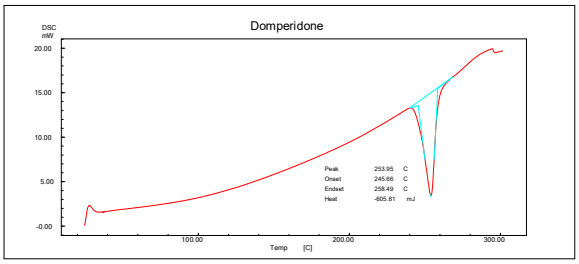


Fig.no.4.DSC Spectrum for Lafutidine

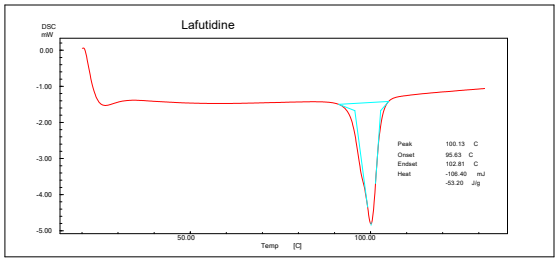


Fig.no.5.DSC Spectrum for Domperidone

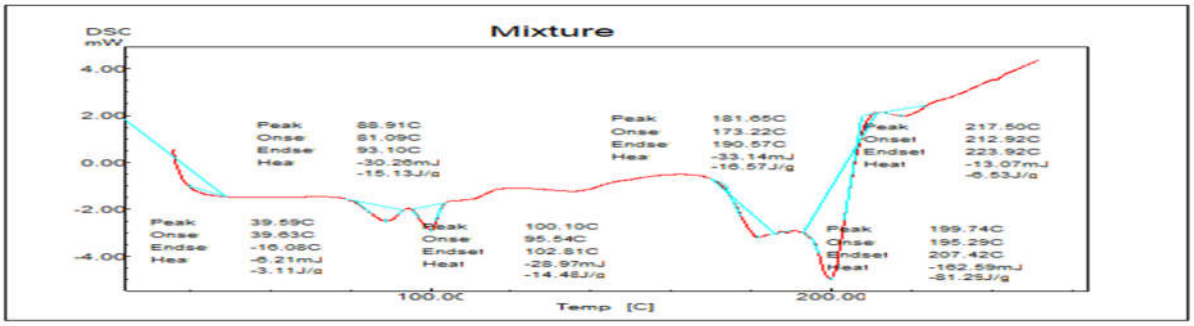


Fig.no.6.DSC Spectrum for Physical Mixture

3.4. In-Vitro dissolution study

The In-Vitro drug release profile is an important tool that predicts in advance how a drug will behave *in vivo*. Release studies are required for predicting the reproducibility of rate and duration of drug release. *In vitro* drug release studies of all the floating tablet formulations were carried out in 0.1 N HCl using USP type II (paddle type) dissolution test apparatus. The study was performed for 12 hrs, and cumulative drug release was calculated at different time intervals.

Table no.4. Buoyancy Floating lag time and Total floating time

Time (Hrs)	% Cumulative drug release for Lafutidine								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	6.19	6.09	5.15	16.18	10.18	9.16	18.97	11.22	10.22
2	13.16	6.20	13.12	20.10	11.13	20.10	20.04	13.12	15.44
3	20.07	13.08	20.07	27.06	13.08	34.04	34.01	26.98	26.98
4	27.04	13.15	20.14	27.13	20.14	34.11	47.54	34.05	34.05
5	27.06	20.06	27.04	34.03	27.04	47.97	54.63	40.98	40.85
6	34.02	27.04	34.02	40.64	33.92	54.89	58.43	47.95	54.94
7	54.13	55.07	41.13	55.10	40.93	56.09	61.91	54.62	62.02

8	61.81	58.46	47.86	58.45	60.78	65.43	68.92	61.79	65.89
9	68.77	65.52	58.67	65.90	66.79	69.60	74.74	68.70	70.81
10	72.40	68.81	61.83	68.75	68.75	74.95	81.34	72.43	74.50
11	75.02	72.24	69.67	80.60	79.25	76.19	84.01	82.85	81.21
12	76.80	73.75	71.79	81.74	80.23	78.38	86.28	83.05	82.51

Table no.4. Buoyancy Floating lag time and Total floating time

Time (Hr)	**% Cumulative drug release for domperidone**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	24.46	22.439	20.38	22.43	21.43	20.37	24.23	20.76	19.43
2	26.44	24.36	24.51	23.88	23.88	25.82	28.07	18.58	22.44
3	28.53	26.17	26.12	25.49	25.49	26.12	30.02	20.47	26.20
4	33.09	28.070	28.00	27.36	24.39	28.0042	33.82	24.34	28.13
5	35.11	28.08	30.05	30.05	29.42	30.05	41.58	28.14	31.96
6	37.84	29.81	31.78	31.78	30.70	31.34	52.61	33.88	37.69
7	43.83	31.80	35.46	39.74	35.46	35.46	58.53	47.55	41.82
8	57.55	52.86	47.04	50.93	39.52	50.69	66.42	54.76	45.43
9	62.72	61.00	58.83	62.59	50.83	62.62	73.85	64.54	51.03
10	70.05	66.56	66.56	66.45	66.45	68.64	77.7	71.95	62.54
11	72.10	71.10	70.26	75.75	73.43	72.03	81.62	77.68	75.73
12	72.23	71.22	70.31	78.87	73.58	72.13	81.96	77.78	76.84

3.5.Optimization of Formulation

Response 1: %CDR of lafutidine

Table no.5. %CDR of lafutidine

Source	Sum of squares	df	mean square	F-Value	P-Value	
Model	71.21	2	35.61	9.47	0.0139	significant
A-HPMC K100 Conc.	67.40	1	67.40	17.93	0.0055	
B-Sodium Bicarbonate Conc.	3.81	1	3.81	1..01	0.3531	
Residual	22.56	6	3.76			
Cor Total	93.77	8				

Fit Statistics of %CDR OF lafutidine

Table no.6. Fit Statistics of %CDR OF lafutidine

Std.Dev	1.94	R^2	0.7594
Mean	79.77	Adjusted R^2	0.6792
C.V.%	2.43	Predicted R^2	0.3989
		Adeq Precision	7.4113

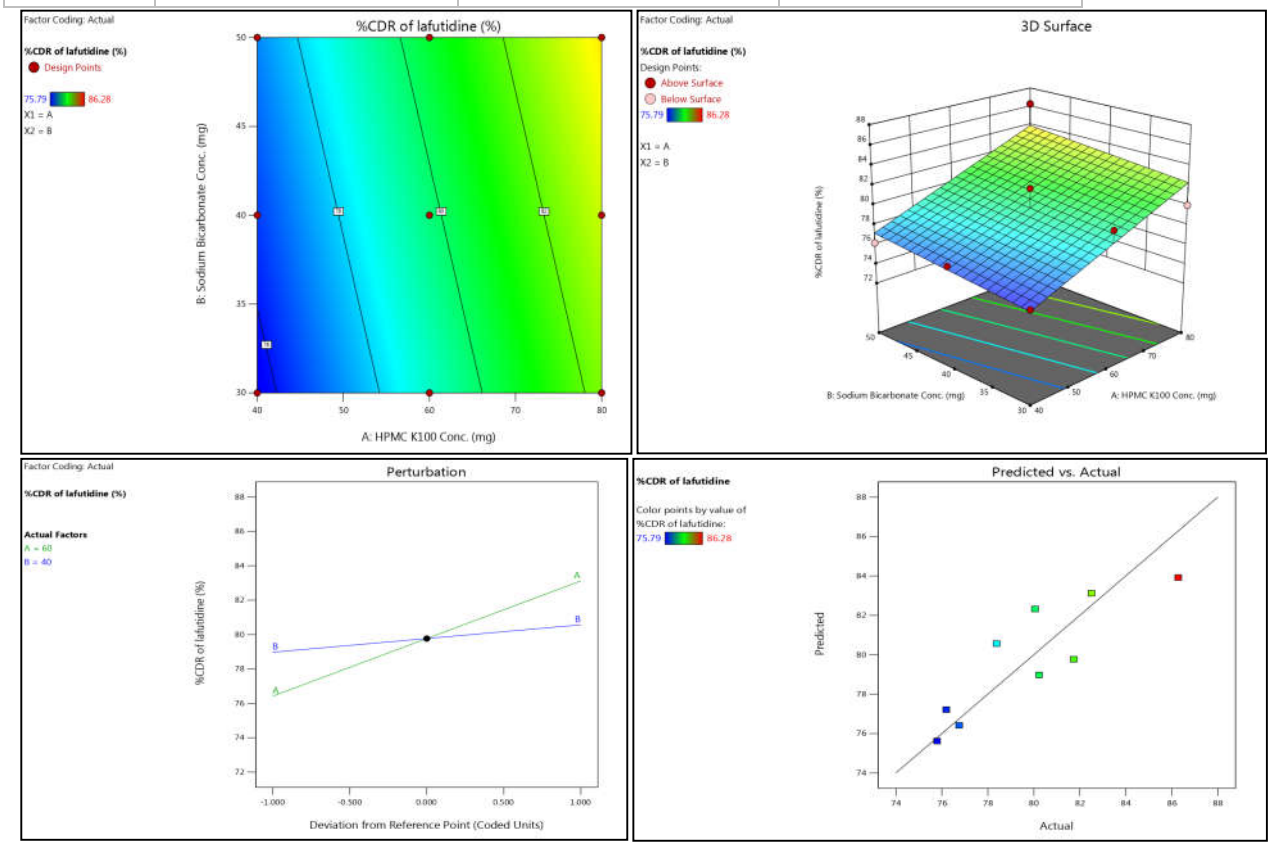


Fig.no.7.Counter Plot for %CDR,3D Plot for %CDR, Perturbation and Predicted Vs Actual graph for %CDR for Lafutidine

Response 2: %CDR of Domperidone

Table no.7. %CDR of Domperidone

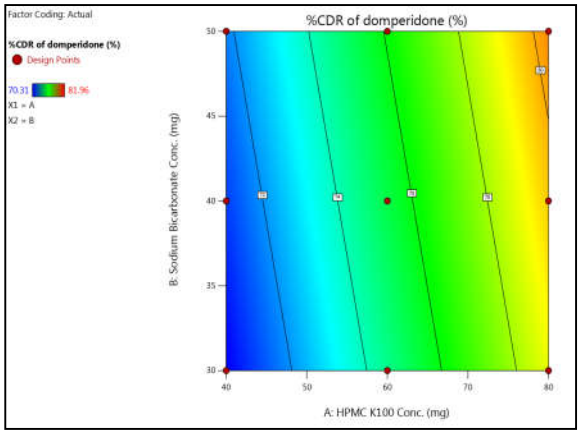
Source	Sum of squares	df	mean square	F-Value	P-Value	
Model	114.72	2	57.36	10.39	0.0112	significant
A-HPMC K100 Conc.	111.11	1	111.11	20.13	0.0042	
B-Sodium Bicarbonate Conc.	3.60	1	3.60	0.6529	0.4499	
Residual	33.12	6	5.52			
Cor Total	147.84	8				

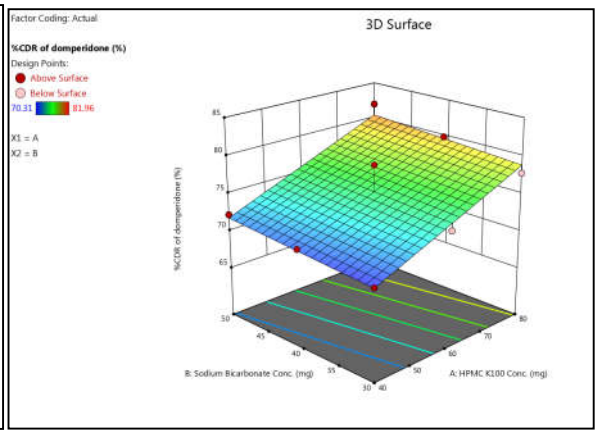
Fit Statistics of %CDR OF domperidone

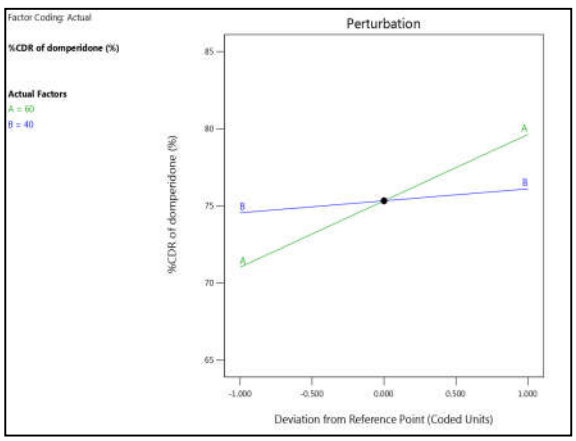
Table no.8. Fit Statistics of %CDR OF domperidone

Std.Dev	**2.35**	**R^2**	**0.7760**
Mean	75.32	Adjusted R^2	0.7013
C.V.%	3.12	Predicted R^2	0.5922
		Adeq Precision	7.4876

%CDR of Domperidone =+75.32+4.30A+0.7750B







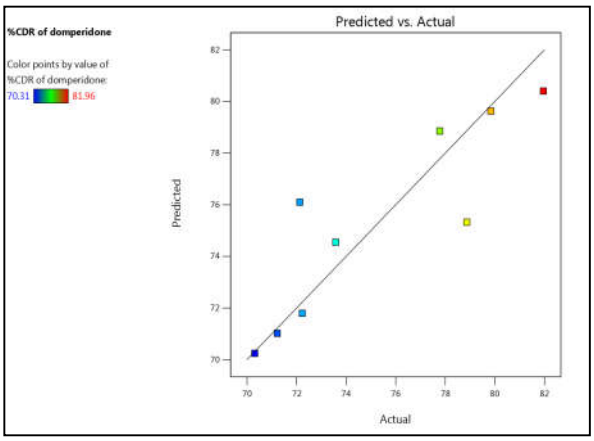


Fig.no.8.Counter Plot for %CDR,3D Plot for %CDR, Perturbation and Predicted Vs Actual graph for %CDR for Domperidone.

Response 3 : Total Floating time

Table no.9 Total Floating time

Source	Sum of squares	df	mean square		P-Value	
Model	8.67	2	4.33		0.0035	significant
A-HPMC K100 Conc.	6.00	1	6.00		0.0030	
B-Sodium Bicarbonate Conc.	2.67	1	2.67		0.0184	
Residual	1.56	6	0.2593			
Cor Total	10.22	8				

Fit Statistics of Total Floating time

Table no.10. Fit Statistics of Total Floating time

Std. Dev	1.94	R^2	0.7594
Mean	79.77	Adjusted R^2	0.6792
C.V.%	2.43	Predicted R^2	0.3989
		Adeq. Precision	7.4113

Total Floating Time =+13.56+1.00A+1.66670B

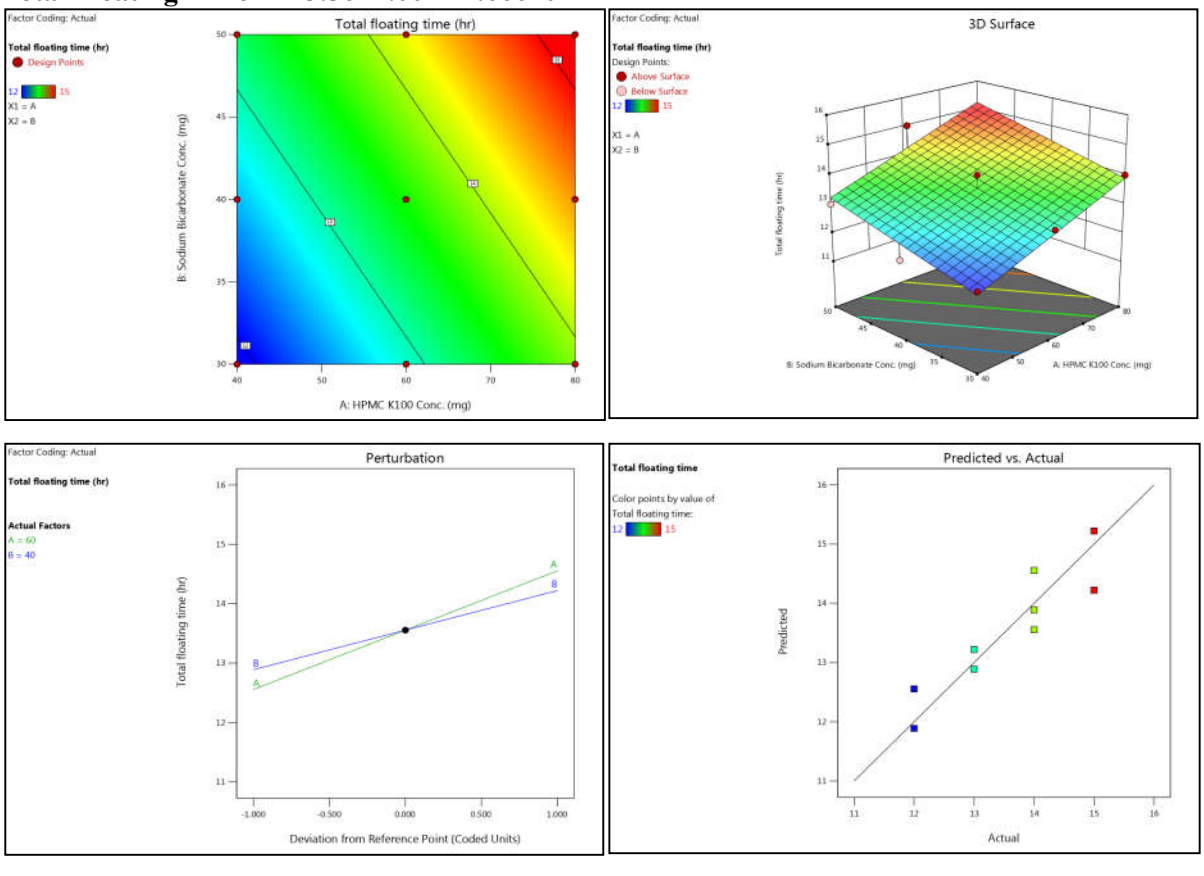


Fig.no.9.Counter Plot for %CDR,3D Plot for %CDR, Perturbation and Predicted Vs Actual graph for Total Floating Time

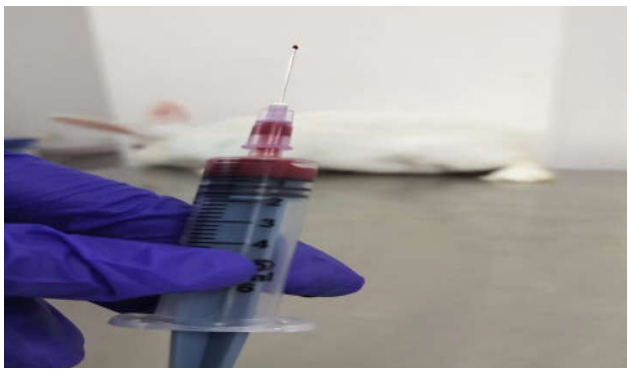
3.6.*In -Vivo Bioavailability* study for floating tablet

Pharmacokinetic parameter of Lafutidine and domperidone after oral administration of lafutidine-domperidone floating tablet formulation (10mg/kg) in albino Wistar rabbit. The graph shows plasma concentration vs. time profiles. In which Cmax determined after administration of marketed formulation was found to be 14.91 µg/ml and 13.74 µg/ml for lafutidine and domperidone respectively and Cmax of floating tablet formulation 20.80 µg/ml and 137.45 µg/ml for lafutidine and domperidone respectively .AUC obtained for marketed formulation to2989.94 µg/ml*h and 2550.86 µg/ml*h for lafutidine and domperidone respectively and for floating tablet formulation 7029.156 µg/ml*h and 32428.02 µg/ml*h for lafutidine and domperidone respectively in which floating tablet formulation shows higher AUC than the Marketed formulation.

DOSING OF STD FORMULATION

DOSING OF TEST SAMPLE

BLOOD COLLECTION IN EAR VEIN



BLOOD SAMPLE

Fig.no.10.*In-vivo* Bioavailability study of Floating tablet

3.7.Conclusion

From the current study it may be found that floating tablet of lafutidine-domperidone has increased bioavailability followed by improving retention time and direct compression method was successful for synthesis floating tablet. Also factorial design was successful in the development of Floating tablet of lafutidine-domperidone. Identification of pure drug and excipients were done by DSC, FTIR, melting point.2 factor 3 level factorial design was used to formulate tablet. Floating tablet was done by direct compression method. As increase in the concentration of HPMC K 100 drug release decreases. As concentration of sodium bicarbonate increases total floating time increases.F7 batch was found be optimized. Preformulation studies shows good result according to USP. *In-vitro* drug release of F7 batch was found to be 86.28%and 81.96% for lafutidine and domperidone respectively. And Total Floating time for F7 was found to be 15 hrs. In the *in-vivo* bioavailability study of formulation shows significant result as compare with pure drug.

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3.9. Reference

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