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"FORMULATION DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING FILMS OF LAFUTIDINE"

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ABSTRACT

The present invention was aimed to formulate and evaluate Lafutidine gastro retentive films. The films were prepared by solvent casting technique using different film forming polymers like HPMC and Ethyl cellulose. PEG 400 used as a plastsizer. The prepared films were evaluated for number of parameters like Physical appearance, Weight variation, Thickness, Folding endurance, Tensile strength, unfolding behavior, floating properties, drug content and In vitro drug release studies. From the trial batches the best release for gastroretentive film was shown by formulation T5 (Ethyl cellulose and PEG 400). Formulation T5 exhibited good appearance, better mechanical strength with acceptable flexibility. Also, formulation T5 was given more than 90 % drug released after 12 hr and 97.56 % Drug content. For optimization of formulation, 3^2 factorial design was applied by taking Ethyl cellulose and PEG 400 as an independent variables. Drug release at 8 hour and folding endurance selected as dependent variables. Based on drug release study, L8 batch found most satisfactory in all formulation and the effect of Ethyl cellulose and PEG 400 found significant. L8 batch found stable during stability study.

Key words: Lafutidine, Floating Films, Ethyl Cellulose.

1. INTRODUCTION

1.1 Introduction of Drug Delivery System

1.1.1 Gastro retentive Dosage Form (GRDF): [1, 2]

A few troubles are looked in structuring continued discharge and controlled discharge frameworks for better assimilation and upgraded bioavailability. One of such troubles is the failure to restrict the measurement frame in the coveted region of the gastrointestinal tract. Gastro retentive frameworks can stay in the gastric locale for a few hours and consequently fundamentally drag out the gastric living arrangement time of medications.

Delayed gastric maintenance enhances bioavailability, lessens medicate wastage, and enhances dissolvability for medications that are less solvent in a high pH condition. GRDF broaden essentially the term of time over which the medications might be discharged. They delay dosing interims, as well as increment understanding consistence. Gastro retentive measurement shapes (GRDF), will achieve new and imperative helpful alternatives, for example,

This application is particularly compelling in sparingly dissolvable and insoluble medications. It is referred to that, as the solvency of a medication diminishes, the time accessible for medication disintegration turns out to be less satisfactory and in this way the travel time turns into a noteworthy factor influencing drug retention. To defeat this issue, erodible, gastro-retentive

measurement frames have been produced that give persistent, controlled organization of sparingly dissolvable medications at the assimilation site.

GRDF incredibly enhances the pharmacotherapy of the stomach through nearby medication discharge, prompting high medication fixation at the gastric mucosa. (e.g. Killing Helicobacter pylori from the sub-mucosal tissue of stomach) making it conceivable to treat gastric and duodenal ulcers, gastritis and oesophagitis, decrease the danger of gastric carcinoma and direct non-fundamental controlled discharge acid neutralizer details (calcium carbonate).

GRDF can be utilized as bearers for medications with alleged ingestion windows. These substances for example antiviral, antifungal and anti-infection operators (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides, antibiotic medications and so on.), are ingested just from unmistakable locales of the GI mucosa.

1.1.2 Basic Gastrointestinal Tract Anatomy and Physiology [3]

The basic comprehension of the life systems and physiological attributes of the human gastrointestinal tract is fundamental for the effective regulation of the gastrointestinal travel time of a medication conveyance framework to guarantee maximal gastrointestinal ingestion of medications.

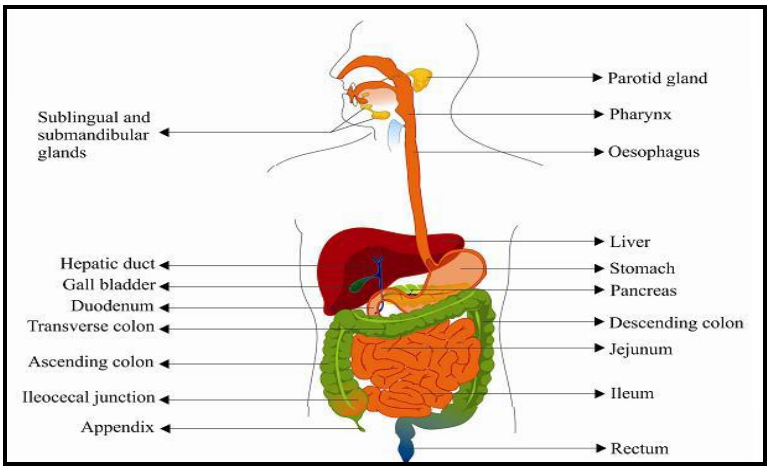


Figure 1: General structure of gastrointestinal tract

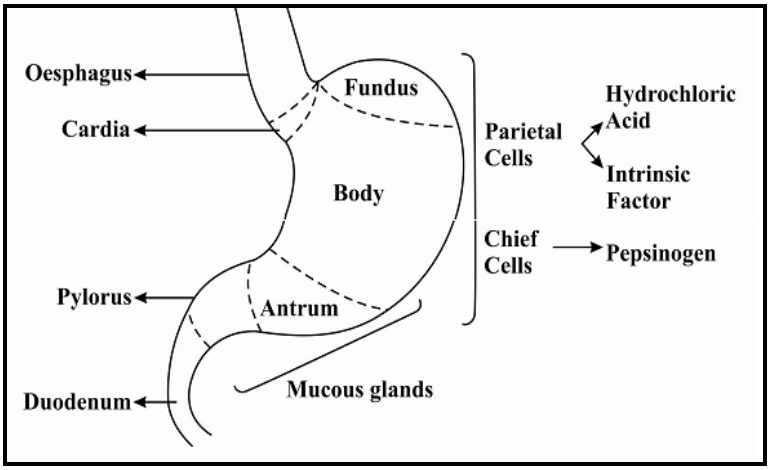


Figure 2: Structure and different regions of stomach

1.1.5 Factors Controlling Gastric Retention Time of a Dosage Form [4-6]

→ Density

→ Size of dosage form

→ Shape of dosage form

→ Single or multiple unit formulation

→ Fed or unfed state: Nature of meal: Caloric content

→ Frequency of feed

→ Age: Posture

→ Concomitant drug administration

→ Biological factors

1.1.6 Advantages of gastro retentive delivery systems :- [7]

✓ Improvement of bioavailability and remedial adequacy of the medications and conceivable decrease of portion e.g. Furosemide

✓ Maintenance of steady restorative levels over a drawn out period and accordingly decrease in change in helpful levels limiting the danger of opposition particularly if there should be an occurrence of anti-microbials. E.g. b-lactam antibiotics(penicillins and cephalosporins)

✓ For drugs with generally short half life, continued discharge may result in a flip-flounder pharmacokinetics and furthermore empower lessened recurrence of dosing with enhanced patient Compliance.

✓ They additionally have leverage over their ordinary framework as it tends to be utilized to conquer the difficulties of the gastric maintenance time (GRT) and additionally the gastric purging time (GET). As these frameworks are relied upon to stay light on the gastric liquid without influencing the inherent rate of utilizing on the grounds that their mass thickness is lower than that of the gastric liquids.

✓ Gastro retentive medication conveyance can create drags out and supports arrival of medications from measurements frames which benefit neighborhood treatment in the stomach and small digestive tract. Thus they are helpful in the treatment of disarranges identified with stomach and small digestive system.

✓ The controlled, moderate conveyance of medication shape gastro retentive measurement frame gives adequate neighborhood activity at the unhealthy site, in this way limiting or wiping out fundamental presentation of medications. This site-particular medication conveyance diminishes unfortunate Effects of reactions.

✓ Gastro retentive dose frames limit the change of medication fixations and impacts. Subsequently, focus subordinate unfavorable impacts that are related with pinnacle fixations can be displayed. This element is of exceptional significance for medication with a restricted restorative record.

✓ Gastro retentive medication conveyance can limit the counter movement of the body prompting higher medication effectiveness.

✓ Reduction of vacillation in medication focus makes it conceivable to acquire enhanced selectivity in receptor initiation.

1.1.7 Limitations of gastro retentive delivery systems :- [8]

✓ Require a larger amount of liquids in the stomach.

✓ Not appropriate for Drugs that Have dissolvability issues in gastric liquid. e.g. phenytoin

✓ Cause G.I bothering. e.g. NSAIDS.

✓ Are flimsy in acidic condition.

- ✓ Drugs planned for particular discharge in the colon e.g. 5-amino salicylic corrosive and corticosteroids and so forth.
- ✓ The drifting frameworks in patients with achlorhydria can be faulty in if there should arise an occurrence of swellable framework.
- ✓ Retention of high thickness frameworks in the antrum part under the moving floods of the stomach is sketchy.
- ✓ The bodily fluid on the dividers of the stomach is in a condition of consistent restoration, coming about a capricious adherence.

1.1.8 Potential drug candidates for stomach specific drug delivery systems :- [9]

- ✓ Drugs those are locally dynamic in the stomach e.g. misroprostol, acid neutralizers and so forth.
- ✓ Drugs that have restricted retention window in gastrointestinal tract (GIT) e.g. L-dopa, Para amino benzoic corrosive, furosemide, riboflavin and so on.
- ✓ Drugs those are temperamental in the intestinal or colonic condition e.g.captopril, ranitidine HCl, Metronidazole.
- ✓ Drugs that exasperate ordinary colonic organisms e.g. anti-toxins against Helicobacter pylori.
- ✓ Drugs that show low solvency at high pH esteems e.g. diazepam, chlordiazepoxide, verapamil HCl.

1.1.9 Drugs those are unsuitable for stomach specific drug delivery systems :- [10]

- ✓ Limited acid solubility e.g. phenytoin etc.
- ✓ Instability in the gastric environment e.g. erythromycin etc.
- ✓ Selective release in the colon e.g. 5- amino salicylic acid, corticosteroids etc.

1.1.10 Approaches to gastric retention or mechanistic aspects of GRDFS: - [10]

a) Floating Systems:

Floating Drug Delivery Systems (FDDS) have a mass thickness lower than gastric liquids and along these lines stay light in the stomach for a drawn out timeframe, without influencing the gastric purging rate. While the framework is gliding on the gastric substance, the medication is discharged gradually at a coveted rate from the framework.

b) High Density Systems:

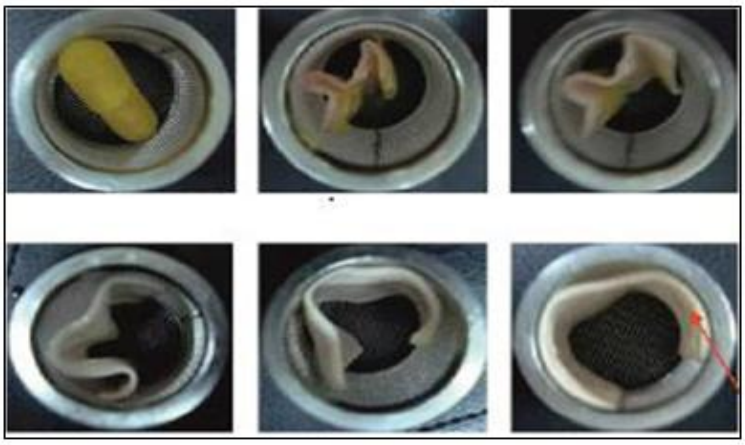
These frameworks with a thickness of around 3 g/cm3 are held in the rugae of the stomach and are fit for withstanding its peristaltic developments. A thickness of 2.6-2.8 g/cm3 goes about as an edge an incentive after which such frameworks can be held in the lower some portion of the stomach.

c) Bio/Muco-adhesive Systems:

Bio/muco-glue frameworks are those which tie to the gastric epithelial cell surface or mucin and fill in as potential methods for expanding the GRT of medication conveyance framework (DDS) in the stomach, by expanding the closeness and term of contact of medication with the natural film.

d) Swelling and Expanding Systems:

These are the measurements frames, which subsequent to gulping; swell to a degree that keeps their exit from the pylorus. These frameworks might be named as "plug type framework", since they show the propensity to remain logged at the pyloric sphincter if that surpass a distance across of around 12-18 mm in their extended state.



Complete Defolding

Figure 3: Expandable dosage form

Expandable gastroretentive measurements shapes (GRDFs) have been intended for as far back as 3 decades. They were initially made for conceivable veterinary utilize, yet later the structure was altered for improved medication treatment in people. These GRDFs are effortlessly gulped and achieve an altogether bigger size in the stomach because of swelling or unfurling forms that drag out their gastric maintenance time (GRT). After medication discharge, their measurements are limited with resulting departure from the stomach. In any case, the dose shape must be little enough to be gulped, and should not cause gastric check either separately or by gathering. Hence, their setups are required to build up an expandable framework to delay gastric maintenance time (GRT):

1. A little arrangement for oral admission,
2. An extended gastro retentive frame, and
3. A last little frame empowering clearing following medication discharge from the gadget.

In this manner, gastro retentivity is enhanced by the blend of considerable measurement with high unbending nature of dose shape to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable frameworks have been examined and as of late attempted to build up a powerful gastroretentive medication conveyance. Unfoldable frameworks are made of biodegradable polymers. Expandable frameworks have a few downsides like problematical stockpiling of much effortlessly hydrolysable, biodegradable polymers moderately fleeting mechanical shape memory for the unfurling framework most hard to industrialize and not savvy. Once more, perpetual maintenance of inflexible, substantial single-unit expandable medication conveyance dose structures may cause brief impediment, intestinal grip and gastropathy.

e) Incorporation of Passage Delaying Food Agents

Nourishment excipients like unsaturated fats e.g. salts of myristic corrosive change and alter the example of the stomach to a sustained state, in this manner diminishing gastric purging rate and allowing impressive prolongation of discharge. The postponement in the gastric exhausting after suppers wealthy in fat is to a great extent caused by immersed unsaturated fats with chain length of C10-C14.

f) Ion-Exchange Resins

Particle trade pitches are stacked with bicarbonate and an adversely charged medication is bound to the gum. The resultant dabs were then epitomized in a semi-penetrable layer to defeat the

quick loss of carbon dioxide. Upon landing in the acidic condition of the stomach, a trade of chloride and bicarbonate particles occurs. Because of this response carbon dioxide was discharged and caught in the film along these lines conveying dots towards the highest point of gastric substance and creating a drifting layer of sap dabs rather than the uncoated dabs, which will sink rapidly.

g) Osmotic Regulated Systems

It is contained an osmotic weight controlled medication conveyance gadget and an inflatable drifting help in a bio-erodible container. In the stomach the case rapidly deteriorates to discharge the intra-gastric osmotically controlled medication conveyance gadget. The inflatable backings inside structures a deformable empty polymeric pack that contains a fluid that gasify at body temperature to expand the sack. The osmotic controlled medication conveyance gadget comprises of two components– sedate repository compartment and osmotically dynamic compartment.

h) pH-Independent formulation

Most medications are either powerless acids or feeble nuts and bolts and henceforth pH subordinate discharge is seen in body liquids. Anyway supports can be added to such details to help in keeping up a consistent miniaturized scale natural pH to acquire pH autonomous medication discharge.

g) Multiple-unit dosage forms

The motivation behind planning numerous unit dose shape is to build up a solid definition that has every one of the upsides of a solitary unit frame and furthermore is without the previously mentioned detriments of single-unit details. Microspheres have high stacking limit and numerous polymers have been utilized, for example, egg whites, gelatine, polymethecrylate, polyacrylamine. Round polymeric microsponges likewise alluded to as "microballoons" have been readied.

1.2 Introduction of Disease

- **Peptic Ulcer** [(11)]

Peptic ulcers are sores that develop in the lining of the stomach, lower esophagus, or small intestine. They're usually formed as a result of inflammation caused by the bacteria H. pylori, as well as from erosion from stomach acids. Peptic ulcers are a fairly common health problem.

There are three types of peptic ulcers:

- **Gastric ulcers:** ulcers that develop inside the stomach
- **Esophageal ulcers:** ulcers that develop inside the esophagus
- **Duodenal ulcers:** ulcers that develop in the upper section of the small intestines, called the duodenum

Causes of peptic ulcers:

Different factors can cause the lining of the stomach, the esophagus, and the small intestine to break down. These include:

- ✓ *Helicobacter pylori* (*H. pylori*), a type of bacteria that can cause a stomach infection and inflammation
- ✓ frequent use of aspirin (Bayer), ibuprofen (Advil), and other anti-inflammatory drugs (risk associated with this behavior increases in women and people over the age of 60)
- ✓ smoking
- ✓ drinking too much alcohol

- ✓ radiation therapy
- ✓ stomach cancer

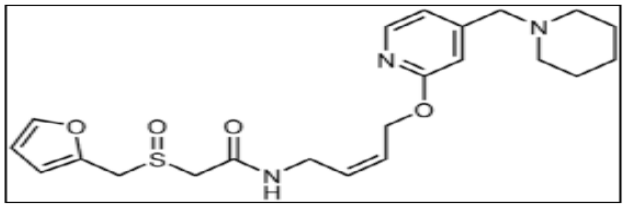
Symptoms of peptic ulcers:

- ✓ Changes In Appetite
- ✓ Nausea
- ✓ Bloody Or Dark Stools
- ✓ Unexplained Weight Loss
- ✓ Indigestion
- ✓ Vomiting
- ✓ Chest Pain

1.3 Introduction of Drug

- **LAFUTIDINE:-**[12-15]

Table 1: Drug Information

General Properties:-	
Name	Lafutidine
Description	Lafutidine is yellowish white crystalline powder
Appearance	Lafutidine is yellowish white crystalline powder
Structure	
CAS number	0118288-08-7
Category	Histamine H_2-receptor antagonist
Molecular Weight	431.55 g/mol
Chemical Formula	$C_{22}H_{29}N_3O_4S$
IUPAC Name	2-[(furan-2-yl)methanesulfinyl]-N-[(2Z)-4-({4-[(piperidin-1-yl)methyl]pyridin-2-yl}oxy)but-2-en-1-yl]ethanimidic acid
Solubility	freely soluble in acetic acid, slightly soluble in methanol, slightly insoluble in ethanol (99.5), very slightly soluble in diethyl ether and practically insoluble in water.
Water Solubility	0.243 mg/ml
Log P	2.79

pKa	2.41
Melting point (°C)	96-99 °C
Hygroscopic	Non hygroscopic
Identification	FTIR, UV, HPLC
BCS Class	II
Dose	10 mg two to three times daily
Pharmacokinetic Properties:-	
Absorption	After oral administration, Lafutidine is rapidly absorbed in the GIT.
Protein binding	99%
Metabolism	It has been reported that CYP3A4 is mainly (CYP2D6 is partially) associated with the metabolism of 23anthan2323a.
Half life	3 hours
Excretion	Lafutidine is mostly excreted in urine as drug metabolites and as unchanged drug, to some extent.
Pharmacological Properties:-	
Indication	Anti-ulcerative agent.
Mechanism of action	Lafutidine has multimodal mechanism of action. Lafutidine not only suppresses gastric acid secretion, but also has cytoprotective properties by the virtue of its property to induce the collagen synthesis in the gastric mucosa.
Marketed Preparations:-	

Brand/Generic Name	Availability	Company Name
Lafudac	Tablet:-10 mg	Unichem Laboratories Ltd
Lafukem	Tablet:-10 mg	Alkem Laboratories Ltd
Lafjoy	Capsule:-10 mg	J B Chemicals Ltd
STOGAR	Tablet:- 5/10 mg	UCB Japan.

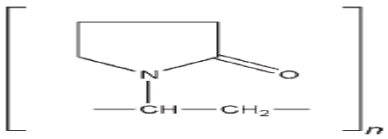
1.4 Introduction of Excipients

- **HYDROXY PROPYL METHYL CELLULOSE (HPMC)** [16]

Nonproprietary Names	:	**BP: Hypromellose** **hyl Hydroxyl Propyl Cellulose** **droxy Propyl Methyl Cellulose**
Synonyms	:	Methocel, HPMC
Chemical Name and CAS Registry Number	:	Cellulose, 2-Hydroxypropyl methyl ether
Empirical Formula	:	HPMC is a partly o-Methylated and o- (2- Hydroxy propylated)
Molecular Weight	:	Approximately 10000 to 1500000
Functional Category	:	Tablet binder, coating agent and film former.
Applications in Pharmaceutical Formulation or Technology	:	HPMC is widely used in oral and topical pharmaceutical formulations. In oral products, it primarily used tablet binder and extended release matrix.

- **PVPK 30** [16]

Nonproprietary Names	:	**BP: Povidone** **JP: Povidone** **PhEur: Povidone** **USP: Povidone**

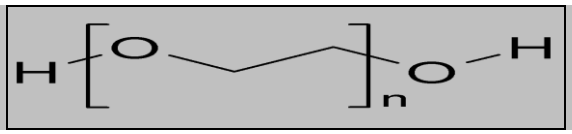
Synonyms	:	E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1- vinyl-2-pyrrolidinone polymer.
Chemical Name and CAS Registry Number	:	1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]
Empirical Formula	:	$(C_6H_9NO)n$
Structural Formula	:	
Functional Category	:	Disintegrant; dissolution enhancer; suspending agent; tablet binder.
Applications in Pharmaceutical Formulation or Technology	:	In spite of the fact that povidone is utilized as a part of an assortment of pharmaceutical plans, it is basically utilized as a part of strong measurement shapes. In tableting, povidone arrangements are utilized as covers in wet-granulation forms. Povidone is additionally added to powder mixes in the dry shape and granulated in situ by the option of water, liquor, or hydroalcoholic arrangements. Povidone is utilized as a solubilizer in oral and parenteral plans, and has been appeared to upgrade disintegration of ineffectively solvent medications from strong dose frames.

- **ETHYL CELLULOSE [16]**

Molecular Formula	**$C_{12}H_{23}O_6(C_{12}H_{22}O_5)nC_{12}H_{23}O_5$**
IUPAC Name	Cellulose ethyl ether
CAS Registry Number	[9004-57-3]
Synonyms	Aquacoat ECD; Aqualon; Ashacel; E462; Ethocel; ethylcellulosum; Surelease.

Appearance	Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder.
Colour	White to tan
Odour	Odorless
Glass transition temperature	129–1338C
Solubility	Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water.

- **Polyethylene Glycol (400)** [16]

Chemical Formula	**$C_{2n}H_{4n+2}O_{n+1}$, n = 8.2 to 9.1**
Synonyms	Polyethylene glycol
Appearance	It is a clear, colorless, viscous liquid.
Structural formula	
Use	Propylene glycol is generally utilized as a plasticizer in watery film-covering plans. Propylene glycol is likewise utilized as a part of beauty care products and in the nourishment business as a transporter for emulsifiers and as a vehicle for flavors in inclination to ethanol, since its absence of instability gives a more uniform flavor.

- **Sodium Bicarbonate** [16]

Nonproprietary Names	:	**BP: Sodium Bicarbonate** **JP: Sodium Bicarbonate** **PhEur: Sodium Hydrogen Carbonate** **USP: Sodium Bicarbonate**
Synonyms	:	Baking soda; E500; Effer-Soda; monosodium carbonate; natrii hydrogenocarbonas; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate

Chemical Name and CAS Registry Number	:	Carbonic acid monosodium salt [144-55-8]
Empirical Formula	:	NaHCO3
Molecular Weight	:	84.01 g/mol
Functional Category	:	Alkalizing agent; therapeutic agent
Applications in Pharmaceutical Formulation or Technology	:	Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation. In effervescent tablets and granules, sodium bicarbonate is usually formulated with citric and/or tartaric acid

METHOD:

4 EXPERIMENTAL WORK

5.1 Characterization of API

5.1.1 Organoleptic property:

This includes recording of colour and odour of the drug using descriptive terminology.

5.1.2 Flow Properties

a) Loose bulk density

Weigh accurately drug (M), which was previously passed through 20 # sieve and transferred in 50 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula:

Bulk density = weight of powder / Bulk volume

b) Tapped bulk density

Weigh accurately drug, which was previously passed through 20 # sieve and transfer in 50 ml graduated cylinder. Then tap the cylinder for 100 times manually and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 100 times and measure the tapped volume (V_2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V_2).Calculate the tapped bulk density in gm/ml by the following formula:

Tapped density = weight of powder / Tapped volume

c) Carr's index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's index (%) = [(TD-BD) x100] / TD

d) Hausner's ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material.

Hausner's ratio = TD / BD

Table 2: Effect of Carr's index and Hausner's ratio on flow property

Carr's index (%)	Flow character	Hausner's ratio
≤ 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45

32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

e) Angle of repose

The angle of repose of API powder was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \phi = h/r$

Where, h and r are the height and radius of the powder cone respectively.

Table 3: Effect of Angle of repose (ϕ) on Flow property

Angle of Repose (Φ)	Type of Flow
< 20	Excellent
20-30	Good
30-34	Passable
>35	Very poor

5.2 Drug Excipient Compatibility studies

5.2.1 Compatibility Studies by FT-IR:-

To investigate any possible interactions between the drug and Excipients used, the FT-IR spectra of pure Lafutidine and its physical mixture (final formulation) with different Excipients were carried out using thermo FTIR spectrophotometer. The samples were prepared as KBr (potassium bromide) disks compressed under a pressure of 150 lbs. The wave number range is selected in between 500 - 3500cm^{-1}.

5.2.2 Identification of drug by DSC:-

Assessment of possible incompatibilities between an active drug substance and its physical mixture (final formulation) an important part of the Preformulation stage during the development of dosage forms. Differential Scanning Calorimeter allows the fast evaluation of possible incompatibilities, because it shows changes in the appearance, shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction.

5.3 Standard calibration curve

Accurately weighed 100 mg of Lafutidine was dissolved in 100 ml of the freshly prepared pH 1.2, 0.1 N HCl to obtain the working standard (i.e. stock solution) of 1000 µg /ml. Aliquots of 1 ml to 6 ml from the above stock solution representing 10 to 60 µg/ml of drug were prepared and transferred to 10 ml volumetric flask. The Volume was adjusted to 10 ml with pH 1.2. Absorbance of the above solutions were taken at 286 nm against the blank solution prepared in the same manner without adding the drug. A graph of absorbance vs. concentration was plotted.

5.4 Solubility study of Lafutidine

The solubility of drug to be determined by taking 10 ml of various medium and then cumulative addition of drug was carried out in order to make saturated drug solution, maintained at 37 °C ± 0.5 °C in a water bath and continually shaken in to mechanical shaker up to 24 h. Samples were withdrawn, filtered through a filter paper suitably diluted and assayed by UV spectrophotometer.

5.5 Dose Calculation

For sustained release dosage form, Dose calculation for 12 hrs calculated by below equation;

$D_T = D_L (1+0.693 \times t/t_{1/2})$

Where,

D_T = Total Dose

D_L = Loading Dose → 5 mg for Lafutidine

t = Time require for drug release → 12 hrs

$t_{1/2}$ = Half life of drug → 3 hrs

$D_T = 5 (1+0.693 \times 12/3)$

= 18.86 mg ≅***19.0 mg of Lafutidine***

Hence the 5 mg of loading dose will release in first hour and remaining amount release in 11 hours.

Table 4: Theoretical drug release profile

Time in hour	mg of drug	% of Drug
1	5	26.3
2	6.3	33.0
3	7.5	39.7
4	8.8	46.4
5	10.1	53.1
6	11.4	59.8
7	12.6	66.5
8	13.9	73.2
9	15.2	79.9
10	16.5	86.6
11	17.7	93.3
12	19.0	100.0

- **Dose Calculation for Film Preparation**

Amount of Drug calculated for formulation purpose. Based on the petridish size it was calculated with the help of diameter of petridish.

Diameter of Petridish (D) = 9.4 cm

Radius of Petridish (r) = 4.7 cm

Area of Petridish (A) = πr^2

$= 3.14 \times (4.7)^2$

$A = 69.36\ cm^2$

Now, if 4 × 2 cm^2 film contains 19.0 mg of Lafutidine,

Than for 69.36 cm^2,

= ***164.73 mg of Lafutidine***

5.6 Preparation of Gastroretentive Films

5.6.1 Method of Preparation:-

The Lafutidine film was prepared by using solvent casting method with various polymers. The amount of Lafutidine in the film was 19 mg in 4X2 cm^2 film piece. An appropriate amount of Lafutidine and sodium bicarbonate was dissolved in a suitable amount of solvent methanol and added to the polymer solution slowly with continuous stirring with magnetic stirrer, when drug-polymer mixture mixed homogeneously then added proper amount of plasticizer with continuous stirring and the resulting solution poured in a Petri dish. Then dried the film and remove film from Petri dish and evaluate it.

Table 5: Trial batch composition of Lafutidine Gastroretentive Films

Ingredients/Film (mg)	T1	T2	T3	T4	T5
Lafutidine	19.0	19.0	19.0	19.0	**19.0**
PVP K30	500	---	---	---	**---**
HPMC 15 cps	---	500	---	---	**---**
HPMC 50 cps	---	---	500	---	**---**
HPMC K4M	---	---	---	500	**---**
Ethyl Cellulose	---	---	---	---	**500**
Sodium Bicarbonate	50	50	50	50	**50**
PEG 400 (ml)	0.5	0.5	0.5	0.5	**0.5**
Methanol (ml)	10	10	10	10	**10**
DCM (ml)	10	10	10	10	**10**

Initially feasibility trial was planned by taking different film forming polymers. PEG 400 selected as a plastsizer. Solvent system selected based on solubility of drug and polymers. Drug was easily soluble in methanol so drug dissolve in methanol and polymer solution prepared in Dichloromethane.

Based on trial batches results, factorial design was applied to optimize the final polymer and plastsizer composition.

3 MATERIALS AND EQUIPMENTS

4.1 List of Materials

Table 8: List of materials

Sr. No.	Material	Function	Sources of Material
1.	Lafutidine	API	Astron Research Centre, Ahmedabad
2.	Polyethylene glycol 400	Plasticizer	ACS Chemicals, Ahmedabad.
3.	HPMC K4M Ethyl Cellulose HPMC 15cps, 50cps PVP K30	Polymer	ACS Chemicals, Ahmedabad.
4.	Sodium Bicarbonate	Floating Agent	ACS Chemicals, Ahmedabad.
5.	Methanol, DCM (Dichloromethane)	Solvent	ACS Chemicals, Ahmedabad.

4.2 List of Equipments

Table 9: List of equipments

Sr. No.	Equipments	Manufacturers
1.	Digital weighing balance	Reptech weighing balance ltd., Ahmadabad
2.	Hot air oven	EIE Instrument Pvt. Ltd. Ahmedabad
3.	Dissolution apparatus	Electro lab ltd, Mumbai
4.	U.V.Visible spectrophotometer	Shimadzu-1601, Kroyoto, Japan.
5.	Infrared spectrophotometer	FTIR 8400S, Shimadzu, Kroyoto, Japan.
6.	Tensile Strength tester	Tinius Olsen (HT400).
7.	Magnetic stirrer	Janki Impex Pvt. Ltd, Ahmedabad
8.	pH Meter	Janki Impex Pvt. Ltd, Ahmedabad
9.	Differential scanning calorimeter	DSC TA-60, M/s Shimadzu

- **3^2 Factorial Design for Optimization of Lafutidine Gastroretentive film**

Factorial design is suitable for exploring quadratic response surface and constructing second order polynomial models. The design consists of replicated center points and the set of points lying at the midpoint of the multidimensional cube that defines the region of interest.

This study investigated utility of a 2-factor, 3-level factorial design and optimization process for films prepared by solvent casting technique. Amounts of Ethyl Cellulose (X1) and PEG 400 (X2) were selected as the independent variables whereas total *Y8 % (amount of drug release after 8 h)* and *folding endurance* were selected as dependent variables. Below table showed the composition and experimental runs as per factorial designs.

Table 10: Factorial batch composition of Lafutidine Gastroretentive Films

Batch	Coded Factors		Actual factors	
	X1	X2	X1	X2
L1	-1	-1	400	0.3
L2	-1	0	400	0.5
L3	-1	1	400	0.7
L4	0	-1	500	0.3
L5	0	0	500	0.5
L6	0	1	500	0.7
L7	1	-1	600	0.3
L8	1	0	600	0.5
L9	1	1	600	0.7

levels of 3^2 Full Factorial Designs			
Independent Factors	Levels		
	Low (-1)	Medium (0)	High (1)
X1= Amount of Ethyl Cellulose (mg) (mg)	400	500	600
X2= Amount of PEG 400 (ml)	0.3	0.5	0.7

Ingredients/Film	L1	L2	L3	L4	L5	L6	L7	L8	L9
Lafutidine(mg)	19.0	19.0	19.0	19.0	19.0	19.0	19.0	**19.0**	19.0
Ethyl Cellulose (mg)	400	400	400	500	500	500	600	**600**	600
Sodium Bicarbonate (mg)	50	50	50	50	50	50	50	**50**	50
PEG 400 (ml)	0.3	0.5	0.7	0.3	0.5	0.7	0.3	**0.5**	0.7
Methanol (ml)	10	10	10	10	10	10	10	**10**	10
DCM (ml)	10	10	10	10	10	10	10	**10**	10

5.7 Evaluation of Gastroretentive Films

- **Physical appearance and surface texture of films**

This parameter was checked simply by visual inspection of films and evaluation of texture by feel or touch.

- **Thickness**

Three films of each formulation were taken and the film thickness was measured by using vernier caliper at different strategic locations (3 locations). Mean thickness of each was calculated.

- **Folding endurance**

Three films of each formulation of 4 cm × 2 cm were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it break. The number of times, the film could be folded at the same place without breaking gives the value of folding endurance. The mean value of three readings was calculated.

- **Weight Variation**

Three films of every formulation were selected randomly and individual weight of each 4 cm × 2 cm film was noted on digital balance. The average weight was calculated.

- **Drug content**

Accurately size 4 cm×2 cm of the films were taken and dissolved in 100 ml of 0.1 N HCl solutions in 100 ml volumetric flask then whole solution was sonicated. After sonication and subsequent filtration, suitable dilutions were made with 0.1 N HCl solutions. The prepared solutions were analyzed by using UV spectrophotometer.

- **Surface pH**

The film to be tested was placed in a test tube and was moistened with 1.0 ml of distilled water and kept for 30 seconds. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation.

- **Swelling index**

Swelling of films was examined for triplicate in 0.1N HCl. After recording the initial weight of a film (W1), it was immersed in medium of temperature 37 ± 1 ^{0}C for 720 min and weighed again (W2). Swelling index (%) = (W2-W1)/W1 x 100.

- **Tensile strength**

The tensile strength of the film was evaluated by using the tensilometer. It consists of two load cell grip, the lower one was fixed and upper one was movable. Film strips with dimension 4×2 cm^2 were fixed between these cell grips and force was gradually applied till the film break. The tensile strength was taken directly from the dial reading in kg.

It is calculated by following equation:

Tensile strength= F/A

Where,

F=Break force,

A=Area of film in cm^2

- **In-vitro unfolding behavior**

The capsules were taken for In-vitro unfolding behavior study in 900 ml 0.1N HCl at 37 ± 0.5 ºC using the dissolution USPXXIII Apparatus1 basket (Electrolab) at 50 rpm. Baskets were removed after 5, 15,30,60,90,120,240,480 and 720 min and the films were examined for their unfolding behavior.

- **Floating characteristics**

Three floating films from each formulation were put in flask containing 250 ml of 0.1 N HCl (pH 1.2). The time taken by the film to come from bottom to top was taken as floating lag time and the duration of time for which the film constantly floated on the surface was noted as total floating time.

- **In -vitro drug release study**

The in vitro drug release study of gastroretentive mucoadhesive film in capsule was carried out in the dissolution USPXXIII Apparatus I basket (Electrolab) 900 ml 0.1 N HCl was used as a

dissolution medium. Temperature was maintained at 37±0.5°C and basket was rotated at the speed of 50 rpm. Drug release was monitored for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hrs. 5 ml of samples was withdrawn at each time intervals and sink condition was maintained by replacing an equal amount of fresh dissolution medium. Samples were filtered and analyzed by UV spectrophotometer.

- **Dissolution kinetics**

The dissolution profile of formulations was subjected to various models such as Zero order kinetics, First order kinetics, Higuchi, Korsmeyer-Peppas and Hixson-Crowell to assess the kinetics of drug release from prepared gastroretentive mucoadhesive film of Lafutidine.

- **Stability Studies**

Stability studies were conducted as per ICH Guidelines. The stability study of final formulation was performed by keeping 4×2 cm^2 films at 40 °C temperature and 75% RH for 1 month. Initial and after 1 month parameters (Drug content, folding endurance and drug release study were compared and results were recorded.

6 RESULTS AND DISCUSSION

6.1 Pre formulation Studies

6.1.1 CHARACTERIZATION OF DRUG (LAFUTIDINE)

Table 11: Characteristic Properties of API Lafutidine

Sr. No.	Characteristic Properties		Observation/Result
1	Organoleptic Characteristics	Colour	Yellowish white
2		Odour	Odorless
4	Flow Properties	Bulk density (g /ml)	0.437
5		Tapped density (g /ml)	0.562
6		Carr's index (%)	22.24
7		Hausner's ratio	1.286
8		Angle of repose (θ°)	34.18 º

The above data of API Characterization shows that the API having a poor flow properties. It's a yellowish white crystalline odorless powder. Film formulation does not require flow properties of API because the API has to dissolve in the appropriate solvent and casting of film done.

6.2 Drug Excipients Compatibility Study

6.2.1 FTIR Study

FTIR Study of Pure drug Lafutidine and Final Formulation done and results attached in below figure 4 and 5. From the below results it concluded that no any interaction found between drug and Excipients.

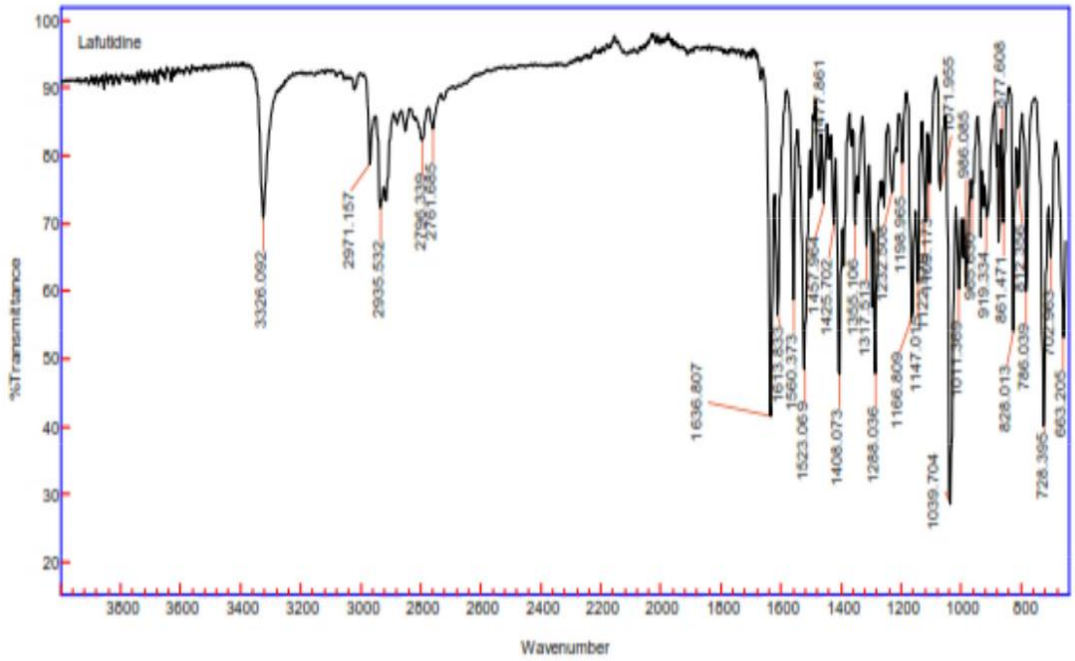


Figure 4: FTIR Spectra of Pure Drug Lafutidine

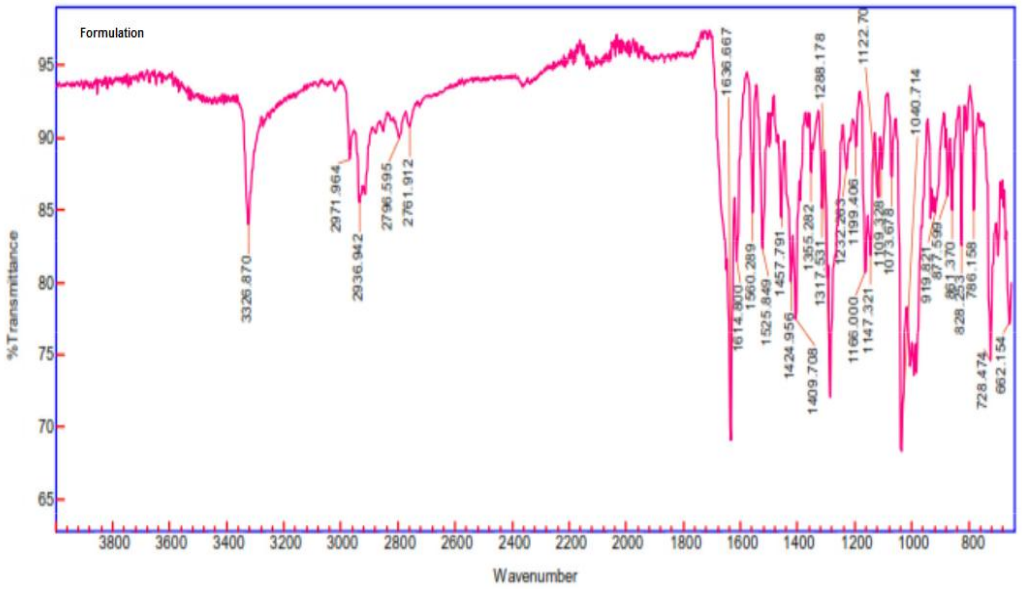


Figure 5: FTIR Spectra of Final Formulation

Table 62: FTIR Data of Lafutidine and Final Formulation

Stretching	Pure Drug Peak (cm^{-1})	Formulation Peak (cm^{-1})
=C-H stretch	3326.09	3326.87
C=O- NH stretch	1636.80	1636.66
S=O stretch	1039.70	1040.71
C-S stretch	728.39	728.47

6.2.2 DSC Study

DSC Study of Pure drug Lafutidine and optimized Formulation performed and results attached in below figure 6 and 7. From the below DSC graph it found that no any drug Excipients interaction in final formulation. Pure drug melting point is 96.0 ^{0}C where in final formulation it's found 97.0 ^{0} C, both are within the melting point range of drug. (96-99^{0}C). It seems that no any interaction found between drug and Excipients.

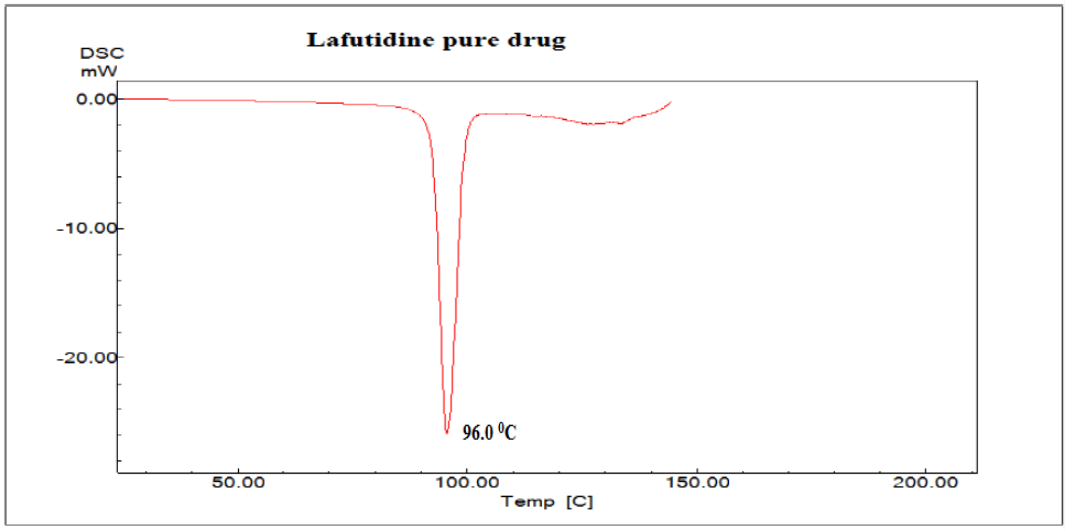


Figure 6: DSC spectra of Pure Drug Lafutidine

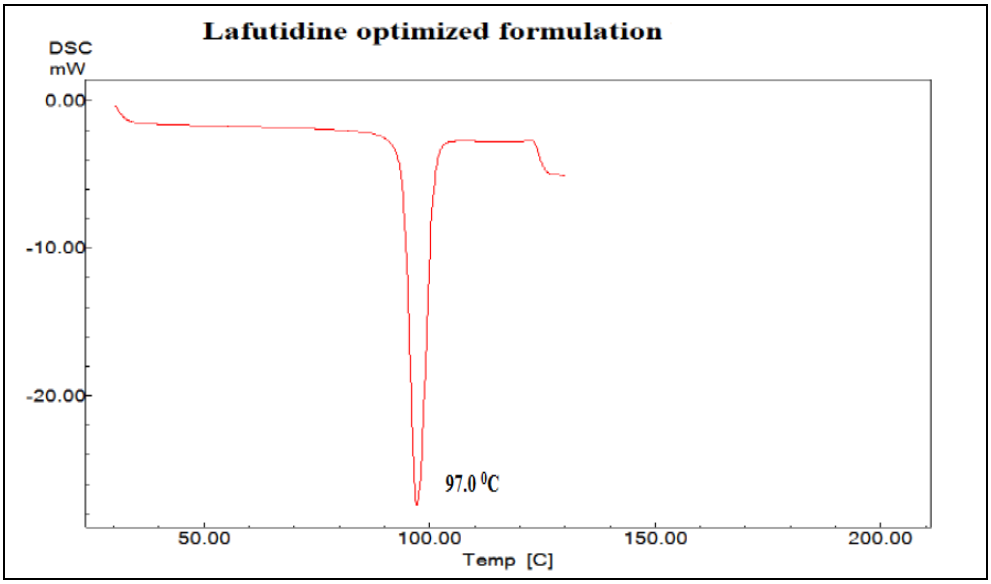


Figure 7: DSC spectra of Optimized Formulation

6.3 Calibration curve of Lafutidine

The calibration curve of Lafutidine was taken to over a concentration range 10-60 µg/ml. (R^2=0.999) the data for calibration curve is given in table 11 and the calibration curve is shown in fig.8.

Table 73: Calibration curve of Lafutidine in 0.1 N HCl at 286 nm

Sr. No	Concentration (µg/ml)	Absorbance ± SD (n=3)
1	0	0
2	10	0.165 ± 0.009
3	20	0.321 ± 0.006
4	30	0.484 ± 0.005
5	40	0.658 ± 0.007
6	50	0.798 ± 0.008
7	60	0.945 ± 0.004

Table 14: Quantitative parameters of Spectrophotometric method

Parameters	Value
λ_{max}	286 nm
Beer's law limits	10-60 µg/ml
Regression equation	y = 0.0158x + 0.0058
R^2	0.9996

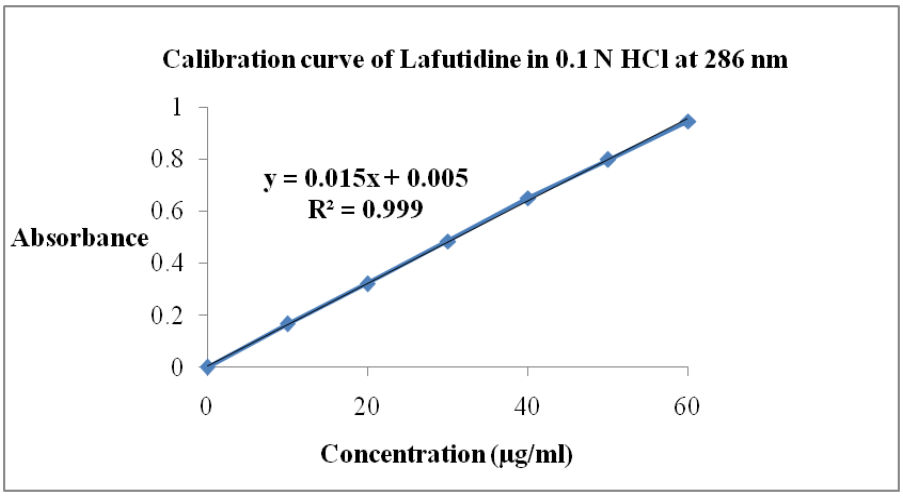


Figure 8: Calibration curve of Lafutidine in 0.1 N HCl at 286 nm

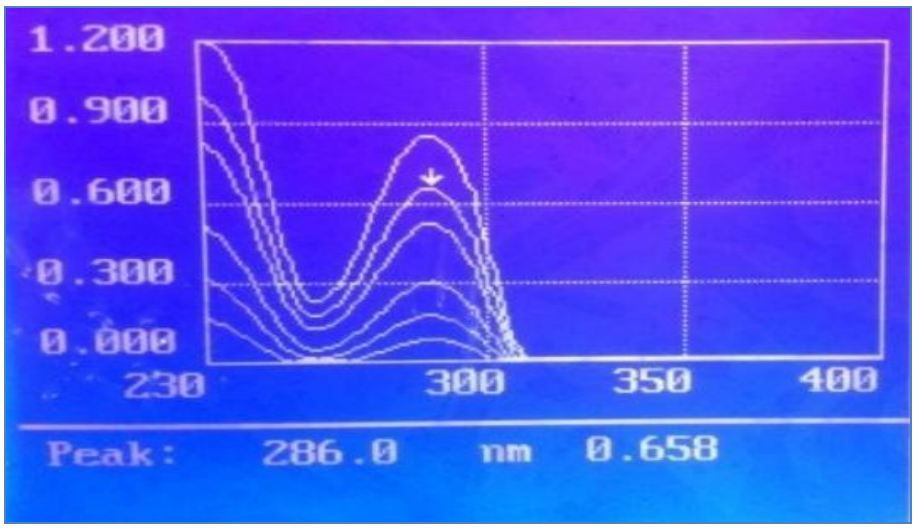


Figure 9: Calibration curve of Lafutidine in 0.1 N HCl at 286 nm

6.4 Solubility study of Lafutidine

The solubility of drug to be determined by taking 10 ml of various medium and then cumulative addition of drug was carried out in order to make saturated drug solution, maintained at 37 °C ± 0.5 °C in a water bath and continually shaken in to mechanical shaker up to 24 h. Samples were withdrawn, filtered through a filter paper, suitably diluted and assayed by UV spectrophotometer. Results are shown in Table 13.

Table15: Solubility of Lafutidine in different solvent

Sr. No	Solvent	Solubility mg/ml
1	Water	0.35 mg/ml
2	0.1 N HCl	12.50 mg/ml
3	Methanol	8.60 mg/ml

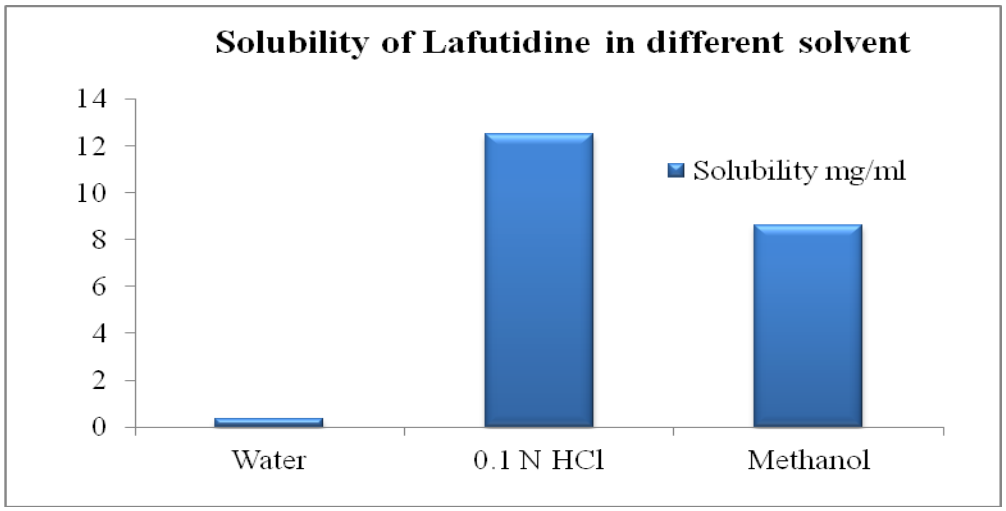


Figure 10: Solubility study of Lafutidine

From the above table it concluded that Lafutidine is freely soluble in Acidic medium so Solubility enhancement is not require for drug. Further the development is Gastroretentive type so in 0.1 N HCl solubility is only important which is good enough to dissolve the drug from the dosage form. Additionally the solubility of drug in methanol was helpful for film preparation by solvent casting method.

6.5 Evaluation of the films of trial batches

Various polymers were evaluated for the preparation of gastro retentive films of Lafutidine. The result of prepared batches was shown in below table. The result revealed that the all selected polymers were suitable for the preparation of film.

Physical appearance and surface texture of films

These parameters were checked simply with visual inspection of films and by feel or touch. The observation reveals that the films of batches T1 to T5 were smooth surface, transparent and they were elegant in appearance.

Weight uniformity of films

The weight of the films was determined using digital balance and the weight uniformity of batches T1 to T5 films were given in below table. The films were found uniform in weight.

Thickness of films

The thicknesses of the films were measured using vernier caliper and the average thickness of batches T1 to T5 films were given in below table. The thicknesses of the films prepared were found to be uniform in all the prepared batches.

Folding endurance of films

The folding endurance gives the idea of flexible nature of films. The folding endurance was measured manually, films were folded repeatedly till it broke, and it was considered as the end point. The folding endurance was found more than 200 in all batches and exhibited good physical and mechanical properties. Ethyl Cellulose batch having highest folding endurance 369 as compared to PVPK 30 and HPMC based films.

Surface pH of films

Surface pH of the films was determined by using pH meter. The surface pH of the batch T1 to T5 was found to be in range of 6.5 to 6.7.

Swelling index of films

The swelling index of batch T1 to T5 was found to be in range of 22.4 to 31.9.

Drug content

The film was dissolved in a 0.1 N HCl in a specific volume. Then the solution was filtered through a whatmann filter medium and analyze the drug contain with the UV method. The result was shown in above Table. The drug content in batches T1 to T5 were in the range of 93.3 to 97.6 % and it shows that the drug was uniformly distributed in films during casting.

Unfolding behavior

Prepared films were evaluated for their in vitro unfolding behavior. The films of PVPK 30 and HPMC based were not unfolded up to 1 hour. Films prepared by ethyl cellulose were unfolded within 15 min. Hence this one was one of the most important parameter for optimization of trial batches.

Floating Lag time and Total floating Time

Prepared films were evaluated for their floating behavior. The films of all trial batches float within 1 min hence the amount of sodium bicarbonate was sufficient to float the film. Films prepared by ethyl cellulose were floated up to 12 hour.

In vitro drug release studies

The in-vitro drug release of batches T1 to T5 were shown in Table 17. Drug release study performed for 12 hour. Films of PVPK 30 gives very fast release as compared to other batches. Further the HPMC based films also not retard the drug release more than 6 hours. Ethyl cellulose batch so called T5 batch release drug up to 12 hours and hence the T5 batch selected for further optimization purpose. It may be due to the ethyl cellulose have a water insoluble polymer and hence it retard the drug release up to 12 hours and others were not.

Hence, the amount of Ethyl Cellulose and Amount of PEG 400 selected as an independent variable for further factorial design application.

Table 86: Evaluation of T1 to T5 batches

Batch	Physical Appearance	Weight Variation (mg)	Thickness (mm)	Folding Endurance
T1	Transparent	512 ± 3	0.80 ± 0.02	241 ± 12
T2	Transparent	515 ± 5	0.78 ± 0.03	256 ± 22
T3	Transparent	519 ± 8	0.75 ± 0.04	268 ± 17
T4	Transparent	505 ± 9	0.70 ± 0.06	270 ± 14
T5	**Transparent**	**513 ± 5**	**0.87 ± 0.02**	**369 ± 15**

Table 97: Evaluation of T1 to T5 batches

Batch	Surface pH	% Swelling Index	Drug content	Unfolding Time (min)
T1	6.7 ± 0.3	22.4 ± 1.12	96.6 ± 0.21	60 min
T2	6.5 ± 0.5	25.6 ± 1.40	93.3 ± 0.12	60 min
T3	6.7 ± 0.1	24.5 ± 0.31	94.0 ± 0.30	60 min
T4	6.5 ± 0.2	31.9 ± 3.12	95.0 ± 0.96	60 min
T5	6.6 ± 0.2	26.0 ± 2.41	97.6 ± 0.21	15 min

Table 108: Evaluation of T1 to T5 batches

Batch	Floating lag time (sec)	Total floating time (h)
T1	54 ± 3.21	5 ± 0.52
T2	59 ± 4.26	6 ± 0.30
T3	62 ± 2.68	8 ± 0.65
T4	56 ± 4.90	9 ± 0.45
T5	**55 ± 2.85**	**12 ± 0.15**

Table 119: Drug release profile of Trial batches T1-T5

Time in hour	T1	T2	T3	T4	T5
0	0	0	0	0	0
1	56.2 ± 1.46	45.1 ± 5.47	36.1 ± 2.54	31.2 ± 6.44	**29.4 ± 3.65**
2	75.9 ± 1.87	61.3 ± 2.14	54.6 ± 3.65	48.7 ± 2.97	**37.4 ± 2.54**
3	84.7 ± 2.98	70.6 ± 6.54	64.8 ± 1.02	58.3 ± 1.54	**45.9 ± 1.98**
4	91.6 ± 3.54	84.3 ± 2.54	78.4 ± 2.62	69.4 ± 3.65	**54.8 ± 6.50**
5	99.9 ± 1.20	93.5 ± 3.03	88.7 ± 3.68	76.1 ± 19.9	**60.9 ± 2.87**
6	-	99.4 ± 3.45	96.3 ± 4.60	82.3 ± 4.60	**68.1 ± 3.12**
7	-	-	98.7 ± 2.75	89.6 ± 1.60	**75.6 ± 2.65**
8	-	-	99.8 ± 3.96	96.7 ± 6.54	**81.3 ± 3.87**
9	-	-	-	99.7 ± 4.68	**88.9 ± 2.90**
10	-	-	-	-	**94.7 ± 1.30**
11	-	-	-	-	**98.2 ± 4.50**
12	-	-	-	-	**99.1 ± 2.87**

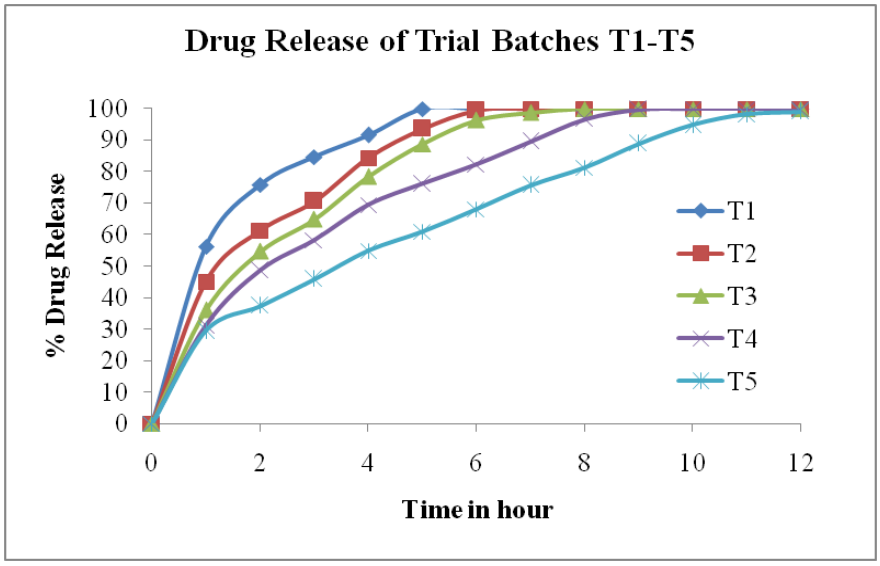


Figure 11: %cumulative drug release of Batch T1 to T5

6.6 Evaluation of the films of factorial batches

Lafutidine loaded films of factorial batches were prepared successfully by solvent casting technique employing PEG 400 as plastsizer and ethyl cellulose as film forming polymer. Films were prepared in rectangular shape of 4X2 cm^2 size.

Each of the film was uniform throughout on basis of its weight. The average weight of film was found to be 415 to 607 mg, respectively, for batches L1-L9. Weight of films was increased as the amount of polymer increased.

Thickness of film for each batch was also found to be significantly uniform throughout. The average thickness of film was found to be 0.78 to 0.98 mm, respectively, for batches L1-L9.

The percentage drug content was also found to be uniform. The average % drug content was noted to be 96.8 to 99.1 % respectively, for batches L1-L9.

The Folding Endurance of the prepared films was evaluated and the results revealed that the amount of polymer is directly correlated to the folding endurance. Lower the amount of polymer lesser the folding endurance. The observed folding endurance was 284 to 390 in batch L1 to L9.

Surface pH of all formulations range between 6.5 - 7.1. Unfolding time was another important evaluation parameter for films. Lower amount of polymer take longer time to unfold and vice-versa. Hence the batches which contain 600 mg of polymer having unfolding time 5 min which was good for the formulation.

Tensile strength of formulations ranges between 0.274 to 0.342 kg/cm^2. Again this parameter was directly impacted by the amount of plastsizer. Higher amount of plastsizer up to some level helps the films flexibility which improves the strength of films. Hence the batch which contains 0.7 ml of PEG 400 gives high tensile strength value.

Swelling index checked for all batches and results of the swelling index revealed that the higher the amount of polymer, the swelling capacity of films higher. The results show that the L1 batch having 18.3 % swelling and L9 batch have 30.3 % swelling.

Table 2012: Evaluation of factorial batches L1-L9

Batch	Appearance	Weigh Variation (mg)	Thickness (mm)	Folding Endurance	Surface pH	Unfolding Time (min)	Tensile Strength (Kg/cm^2)	% Swelling index	% Drug Content
L1	Transparent	415 ± 3	0.78 ± 0.01	284 ± 10	6.7 ± 0.3	30	0.274 ± 0.05	18.3 ± 2.13	98.5 ± 1.90
L2	Transparent	417 ± 7	0.76 ± 0.04	296 ± 14	6.9 ± 0.2	30	0.294 ± 0.04	18.6 ± 1.19	97.9 ± 2.15
L3	Transparent	420 ± 4	0.79 ± 0.08	275 ± 09	7.1 ± 0.1	30	0.31 ± 0.06	18.1 ± 3.12	96.8 ± 3.14
L4	Transparent	511 ± 9	0.81 ± 0.09	321 ± 12	6.5 ± 0.7	15	0.287 ± 0.04	24.3 ± 2.15	97.2 ± 1.95
L5	Transparent	513 ± 6	0.83 ± 0.10	354 ± 16	6.7 ± 0.2	15	0.301 ± 0.03	26.5 ± 1.96	98.3 ± 1.60
L6	Transparent	518 ± 7	0.82 ± 0.03	317 ± 13	6.8 ± 0.4	15	0.321 ± 0.05	26.8 ± 2.95	98.9 ± 1.36
L7	Transparent	612 ± 10	0.94 ± 0.04	384 ± 08	6.7 ± 0.2	5	0.309 ± 0.06	29.1 ± 1.45	99.1 ± 2.60
L8	**Transparent**	**616 ± 8**	**0.97 ± 0.05**	**412 ± 06**	**7.0 ± 0.2**	**5**	**0.336 ± 0.04**	**30.5 ± 3.54**	**97.6 ± 2.10**
L9	Transparent	617 ± 3	0.98 ± 0.04	390 ± 15	6.9 ± 0.4	5	0.342 ± 0.07	30.3 ± 4.10	98.4 ± 3.25

The sodium bicarbonate present in the matrix of film reacts in the acidic environment of the gastric fluid and generates CO_2. Thus the generated gas entraps in the matrix of film as micro bubble which imparts buoyancy in the film. Floating lag time for drug loaded floating film was found to be ranging from 49 to 60 s. It was observed that on increasing the ratio of ethyl cellulose the floating lag time also increased. It may be attributed to delayed penetration of 0.1 N HCl in film matrix due to increased thickness of film. Total floating time of film was found up to 12 hour in all formulation, which could be considered for complete release of drug in stomach.

Table 2113: Evaluation of factorial batches L1-L9

Batch	Floating lag time (sec)	Total floating time (h)
L1	49 ± 2.50	12 ± 0.10
L2	52 ± 3.15	12 ± 0.26
L3	50 ± 1.74	12 ± 0.19
L4	53 ± 2.17	12 ± 0.25
L5	56 ± 3.95	12 ± 0.32
L6	54 ± 2.25	12 ± 0.29
L7	58 ± 3.30	12 ± 0.34
L8	**60 ± 2.78**	**12 ± 0.17**
L9	57 ± 1.98	12 ± 0.12

The drug release from film was also studied in 900 ml, 0.1 N HCl at 37 °C up to 12 h. It was observed that as the amount of polymer increases in film matrix the release decreases significantly. This may be due to the fact that on increasing the polymer amount the film matrix got thicker and the drug molecules took more time to diffuse from the matrix. The release profile data of all the developed formulations were fitted in kinetic model. The best model was selected on the basis of goodness of fit the values of residual sum of squares (RSS).

Table 2214: Drug Release of factorial batches L1-L9

Time in Hour	L1	L2	L3	L4	L5	L6	L7	L8	L9
0	0	0	0	0	0	0	0	**0**	0
1	38.1 ± 4.8	35.9 ± 1.9	34.1 ± 6.9	32.5 ± 5.4	30.1 ± 5.4	27.1 ± 5.6	29.4 ± 3.7	**25.8 ± 2.9**	23.1 ± 3.4
2	45.3 ± 2.9	42.6 ± 3.5	40.3 ± 5.4	40.2 ± 3.3	37.2 ± 3.4	34.3 ± 2.3	35.6 ± 3.6	**32.7 ± 3.5**	29.4 ± 2.9
3	53.6 ± 5.4	50.1 ± 2.4	48.3 ± 5.4	48.1 ± 4.7	45.1 ± 3.9	42.1 ± 3.5	43.6 ± 2.9	**40.5 ± 3.4**	38.4 ± 3.4
4	61.3 ± 6.7	58.9 ± 1.7	55.6 ± 3.3	55.6 ± 6.6	53.2 ± 2.8	50.3 ± 2.9	47.9 ± 5.8	**45.9 ± 2.9**	42.5 ± 1.9
6	78.2 ± 5.9	74.3 ± 3.9	71.2 ± 2.8	72.3 ± 5.4	69.4 ± 1.8	65.8 ± 5.4	65.4 ± 4.6	**61.5 ± 1.8**	59.4 ± 8.4
8	90.1 ± 2.7	86.4 ± 5.6	84.3 ± 3.6	85.3 ± 3.6	82.1 ± 6.5	79.2 ± 6.2	78.5 ± 2.9	**74.6 ± 6.5**	71.2 ± 6.4
10	99.9 ± 0.7	99.2 ± 4.4	98.5 ± 1.1	96.9 ± 1.9	95.1 ± 2.5	93.2 ± 3.6	93.5 ± 2.4	**88.8 ± 3.4**	85.8 ± 7.5
12	99.9 ± 0.5	99.9 ± 0.9	99.5 ± 0.5	99.1 ± 0.4	99.2 ± 3.3	98.2 ± 1.2	99.8 ± 1.2	**99.4 ± 3.8**	97.1 ± 2.3

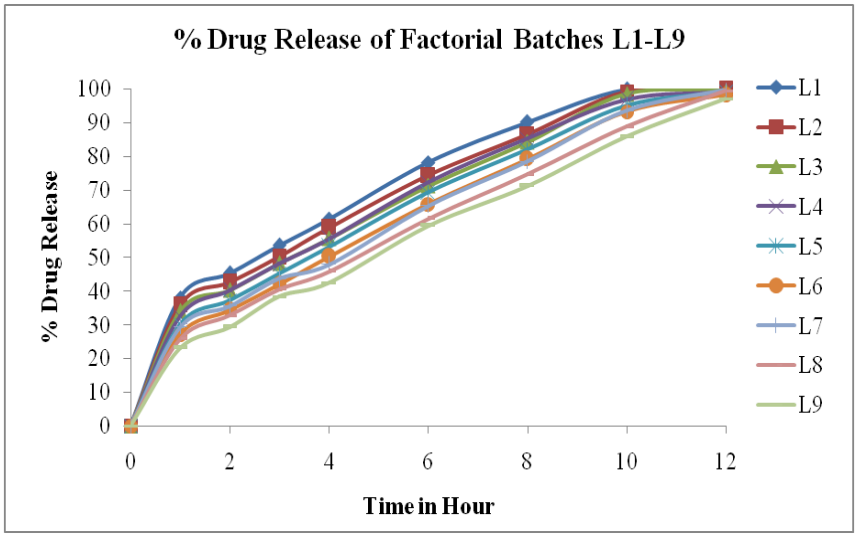


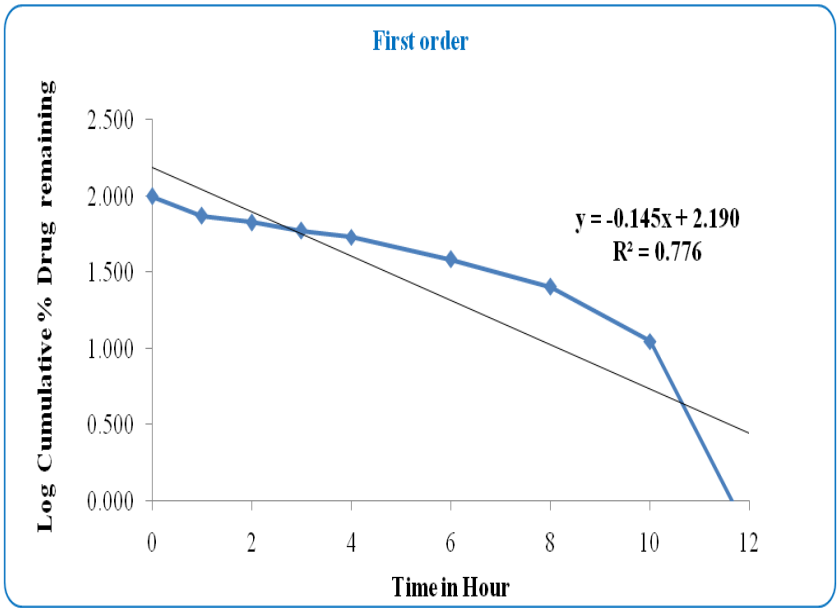
Figure 12: Drug release of factorial batch L1 to L9

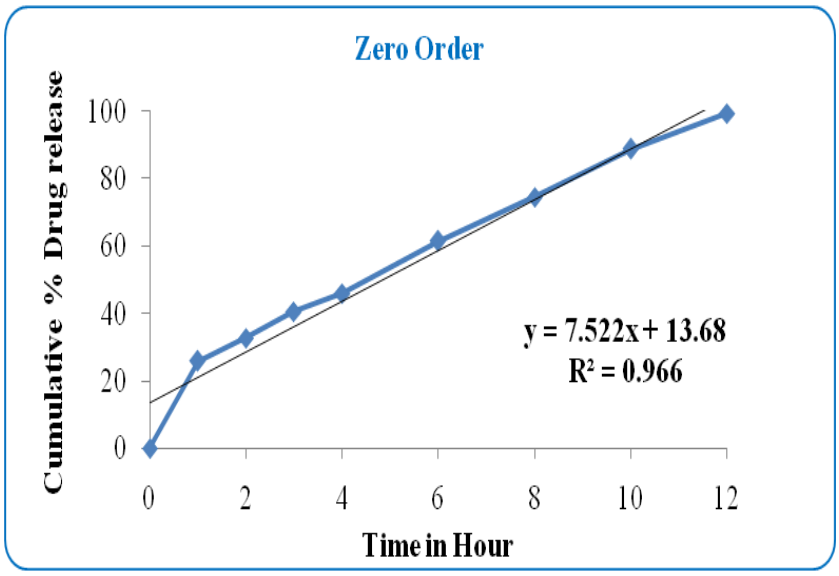
Drug release kinetic study of optimized batch performed by fitting the dissolution data in kinetic model and the results showed in below table.

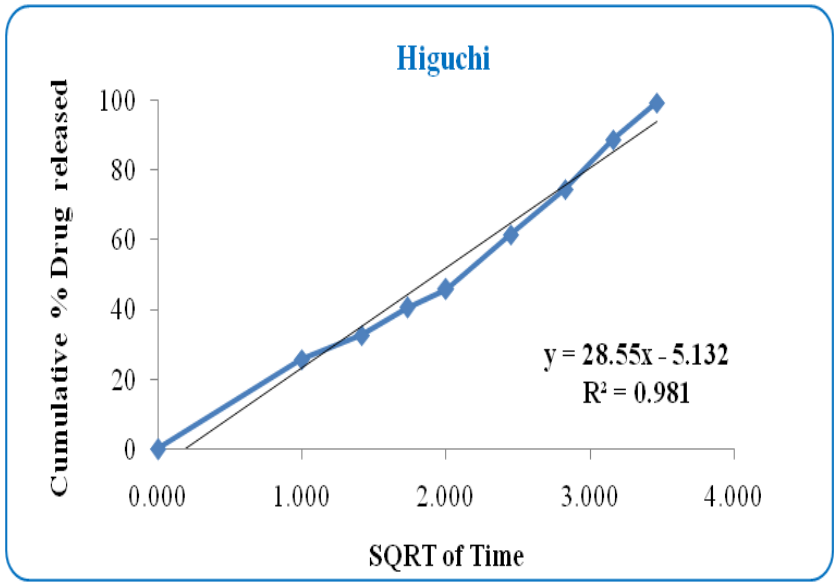
Table 2315: Correlation coefficient (R^2) and constant (K) of different kinetic models of drug release of formulation L8

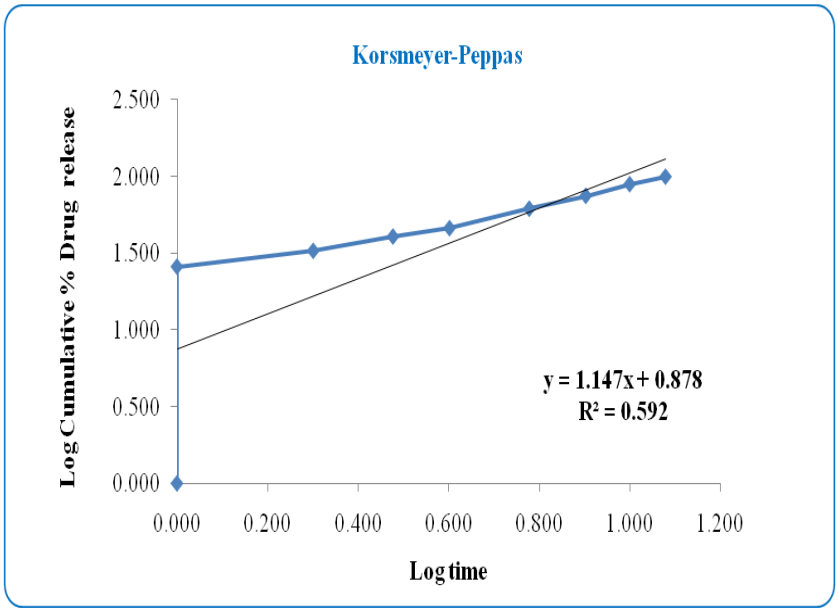
Kinetic Model	Parameters	Value
Zero Order	R^2	0.966
	K_0	13.68
First Order	R^2	0.776
	K_1	2.190
Higuchi	R^2	0.981
	K_H	5.132
Korsmeyer-Peppas	R^2	0.592
	K_P	0.878
Hixon Crowell	R^2	0.930
	K_{HC}	0.083

From the results of release kinetic study it concluded that the formulation follow Higuchi model as the value id 0.981 which was closest value among all the kinetic models. The different model graphs also plotted and showed in below figures.




Zero Order
Cumulative % Drug release
100
80
60
40
20
0
0
2
4
6
8
10
12
Time in Hour
y = 7.522x + 13.68
R² = 0.966


Higuchi
Cumulative % Drug released
100
80
60
40
20
0
0.000
1.000
2.000
3.000
4.000
SQRT of Time
y = 28.55x - 5.132
R² = 0.981


Korsmeyer-Peppas
Log Cumulative % Drug release
2.500
2.000
1.500
1.000
0.500
0.000
0.000
0.200
0.400
0.600
0.800
1.000
1.200
Log time
y = 1.147x + 0.878
R² = 0.592

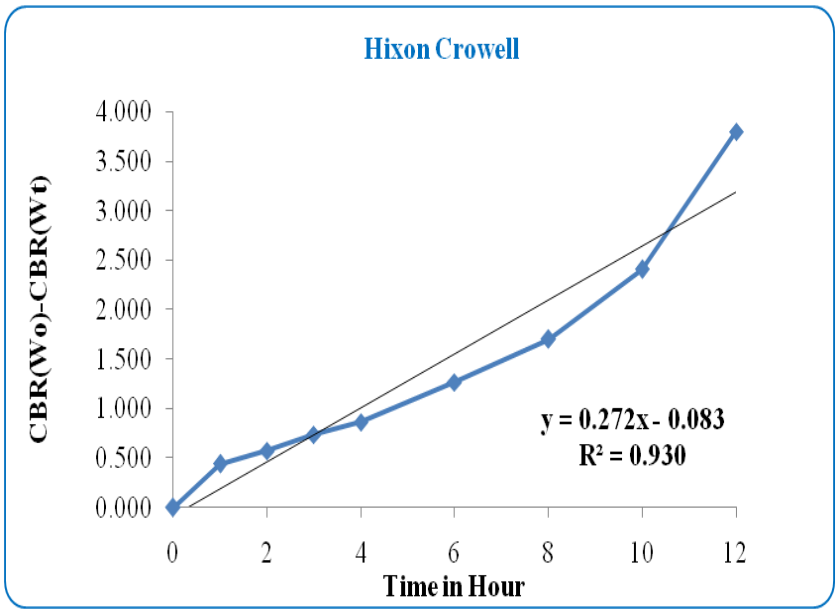


Figure 13: Different release kinetic model plots of formulation L8

6.7 Analysis of Factorial Design

The factorial design was applied using Minitab 16 software by free trial version. For analysis purpose following data fitted in to software and 3^2 design selected.

Table 164 Factorial design table

Batch	Coded Factors		Actual factors		Response	
	X1	X2	X1	X2	Y1	Y2
L1	-1	-1	400	0.3	284	90.1
L2	-1	0	400	0.5	296	86.4
L3	-1	1	400	0.7	275	84.3
L4	0	-1	500	0.3	321	85.3
L5	0	0	500	0.5	354	82.1
L6	0	1	500	0.7	317	79.2
L7	1	-1	600	0.3	384	78.5
L8	1	0	600	0.5	412	74.6
L9	1	1	600	0.7	390	71.2

levels of 3^2 Full Factorial Designs

Independent Factors	Levels		
	Low (-1)	Medium (0)	High (1)
X1= Amount of Ethyl Cellulose (mg)	400	500	600
X2= Amount of PEG 400 (ml)	0.3	0.5	0.7

Dependent Factors

Y1=Folding Endurance

Y2=% Drug release at 8 hour

After fitting of data in Minitab 16, regression analysis was done and the outcome of this analysis showed below.

Table 175 Analysis of Variance for Folding Endurance

Source	DF	Seq SS	Adj SS	F value	P value	Remarks
Main Effects	2	18268.3	18268.3	28.59	0.002	***Significant***
Ethyl Cellulose (mg)	1	18260.2	18260.2	57.16	0.001	***Significant***
PEG 400 (ml)	1	8.2	8.2	0.03	0.879	*Non-Significant*
2-Way Interactions	1	56.2	56.2	0.18	0.692	*Non-Significant*
Ethyl Cellulose (mg) * PEG 400 (ml)	1	56.2	56.2	0.18	0.692	*Non-Significant*
Residual Error	5	1597.4	1597.4	-	-	-
Total	8	19922.0	-	-	-	-

ANOVA table for Folding Endurance shows that the Ethyl Cellulose have a significant impact on folding endurance. PEG 400 have non-significant impact on folding endurance.

Table 186 Estimated Coefficients for Folding Endurance

Term	Co efficient
Constant	110.958
Ethyl Cellulose (mg)	0.457917
PEG 400 (ml)	-99.583
Ethyl Cellulose (mg) * PEG 400 (ml)	0.187500

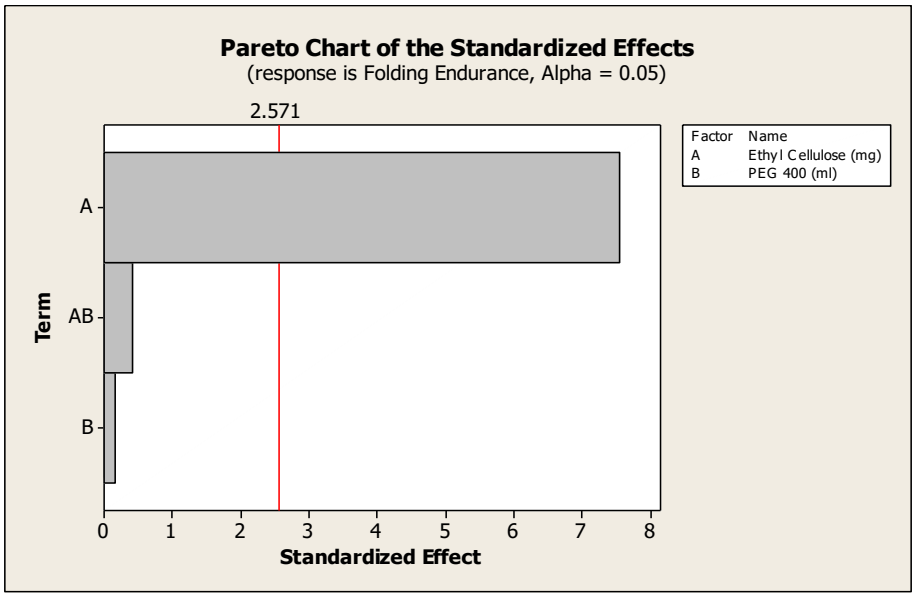


Figure 14: Pareto chart for Folding Endurance

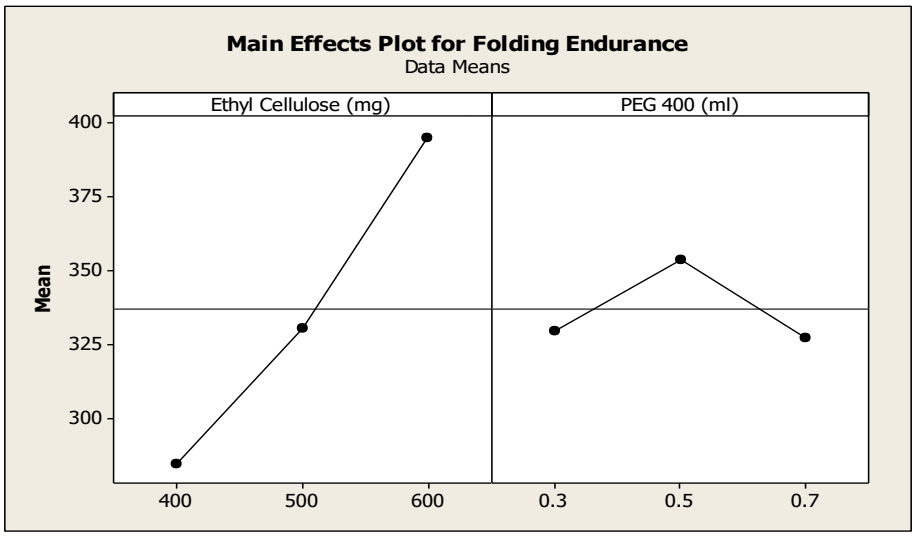


Figure 15: Main effect plot for Folding Endurance

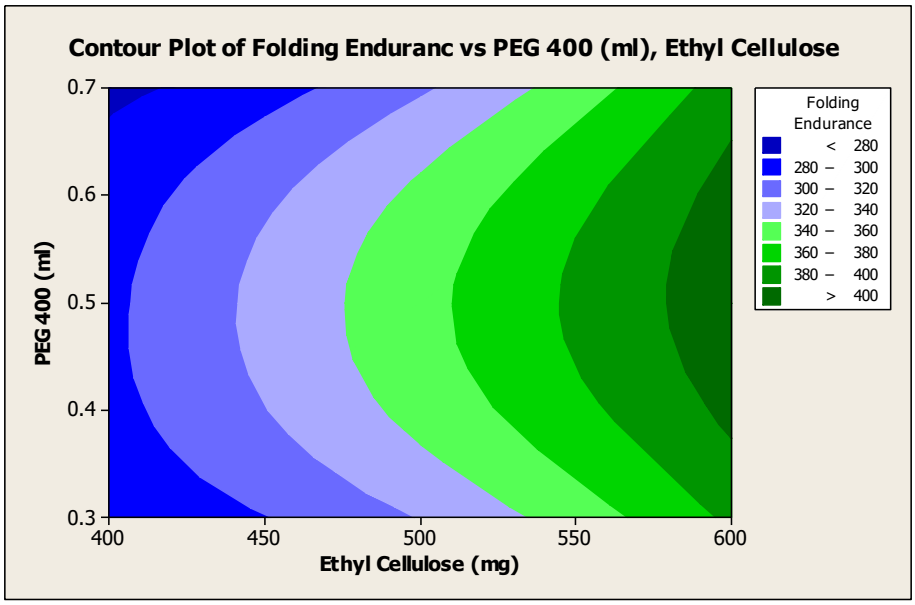


Figure 16: Counter plot for Folding Endurance

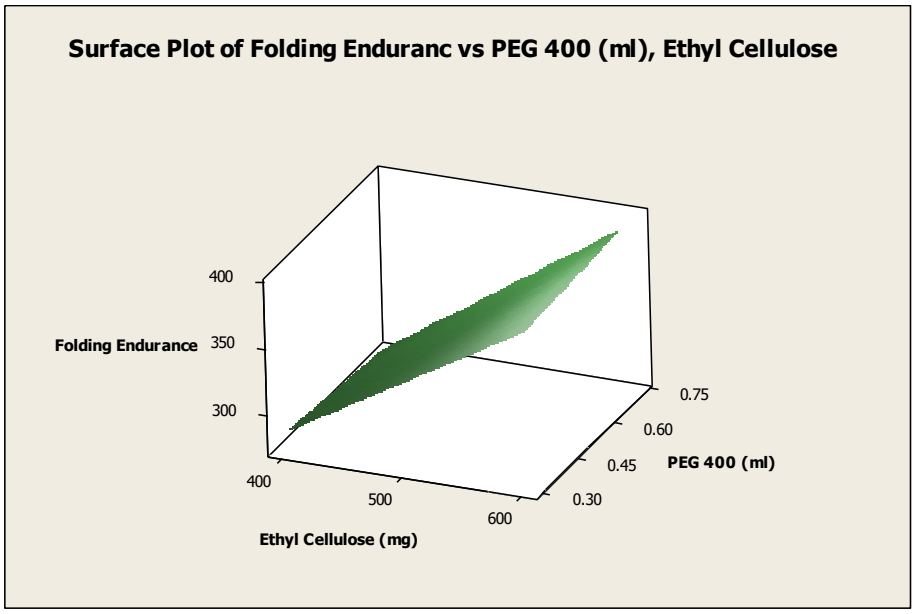


Figure 17: Surface plot for Folding Endurance

Table 197 Analysis of Variance for % Drug release at 8 hour

Source	DF	Seq SS	Adj SS	F value	P value	Remarks
Main Effects	2	283.482	283.482	168.91	0.000	***Significant***
Ethyl Cellulose (mg)	1	222.042	222.042	264.60	0.000	***Significant***
PEG 400 (ml)	1	61.440	61.440	73.22	0.000	***Significant***
2-Way Interactions	1	0.562	0.562	0.67	0.692	*Non-Significant*
Ethyl Cellulose (mg) * PEG 400 (ml)	1	0.562	0.562	0.67	0.692	*Non-Significant*
Residual Error	5	1.196	1.196	-	-	-
Total	8	288.240	-	-	-	-

ANOVA table for % Drug release at 8 hour shows that the Ethyl Cellulose and PEG 400 both have a significant impact.

Table 208 Estimated Coefficients for % Drug release at 8 hour

Term	Co efficient
Constant	115.029
Ethyl Cellulose (mg)	-0.0514583
PEG 400 (ml)	-6.6250
Ethyl Cellulose (mg) * PEG 400 (ml)	-0.0187500

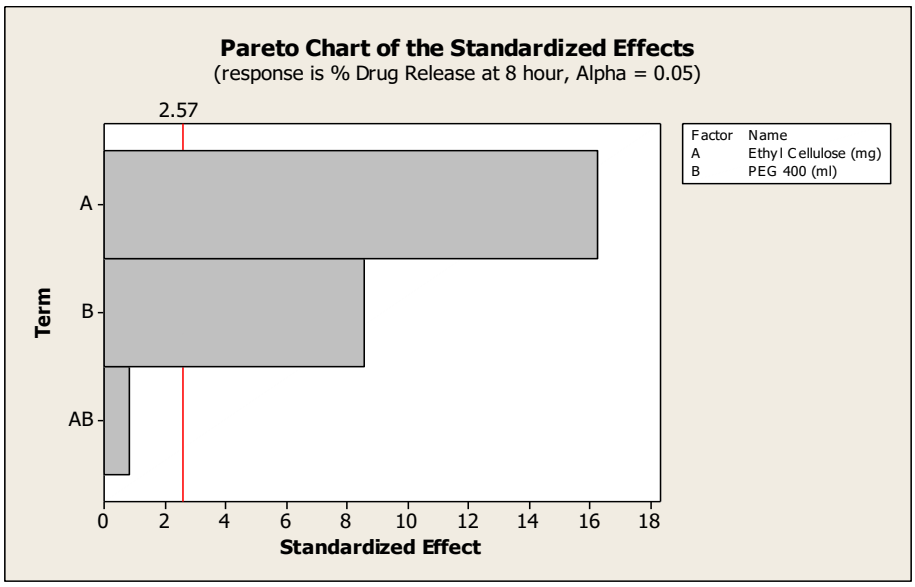


Figure 18: Pareto chart for Drug release at 8 hour

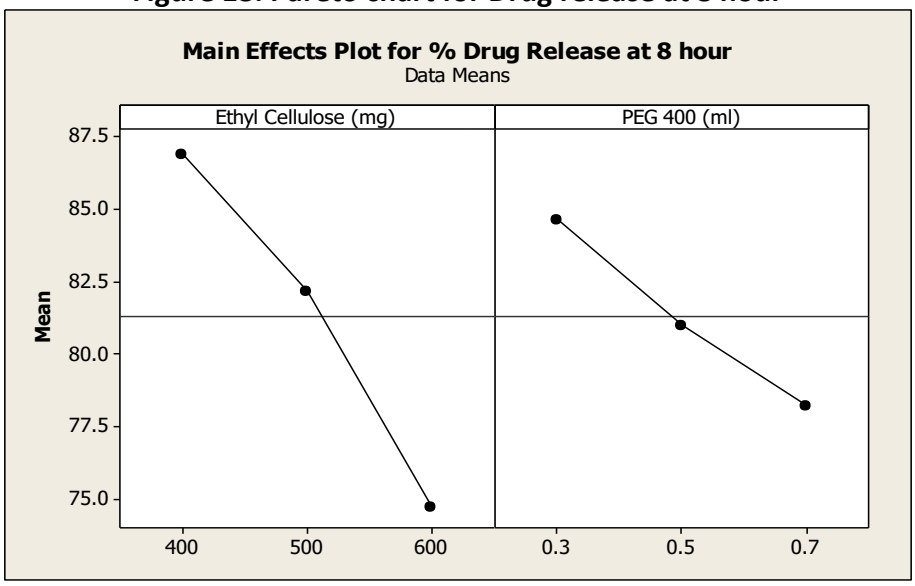


Figure 19: Main effect plot for Drug release at 8 hour

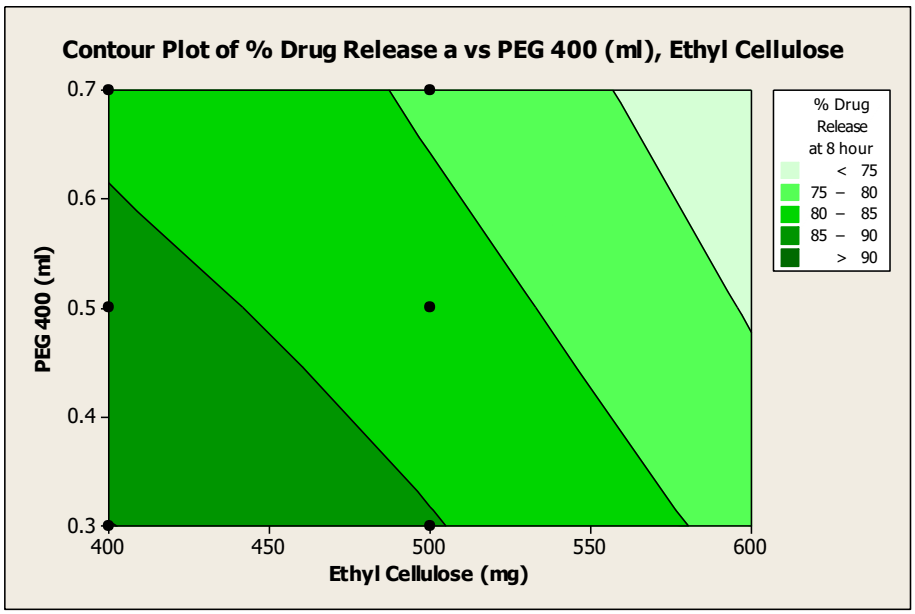


Figure 20: Counter plot for Drug release at 8 hour

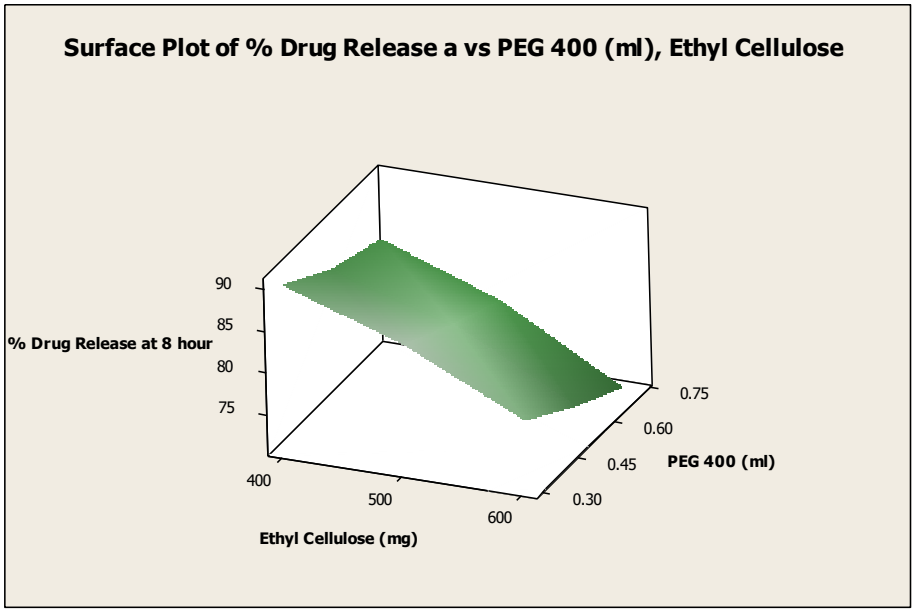


Figure 21: Surface plot for Drug release at 8 hour

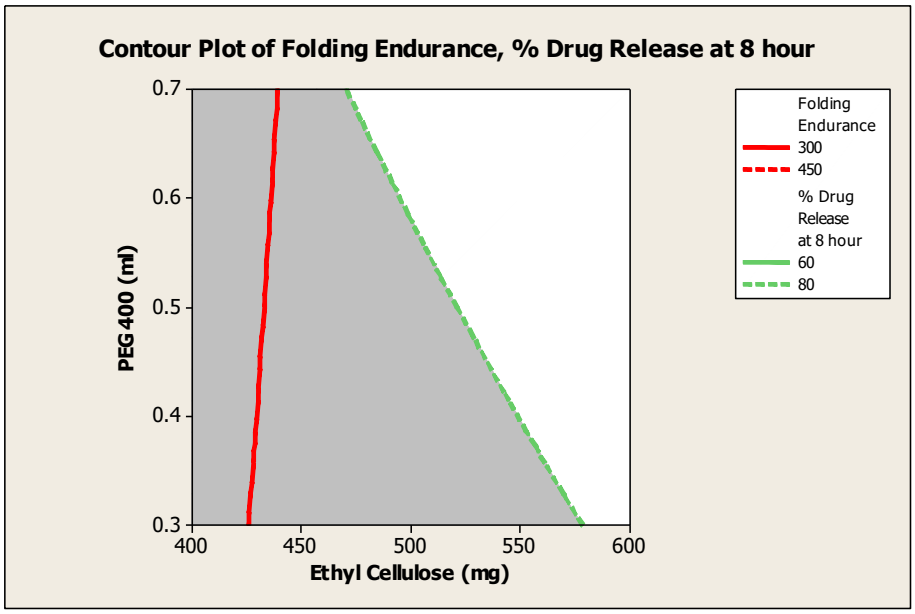


Figure 22: Overlay counter plot

6.8 Stability Study

Stability study of final optimized batch L8 performed for 1 month at 40°C and 75% RH. Initial results and after 1 month results compared and found satisfactory. The batch was found stable during stability. The results were recorded in below table.

Table 219 Stability study data of batch L8

Parameter	Initial	After 1 Month
Appearance	Transparent Film	Transparent Film
Average Weight (mg)	616 ± 8	614 ± 6
Thickness (mm)	0.97 ± 0.05	0.97 ± 0.09
Folding Endurance	412 ± 06	408 ± 04
Unfolding Time (min)	5	5
Floating lag time (sec)	60 ± 2.78	63 ± 1.96
Total floating time (h)	12 ± 0.17	12 ± 0.08
% Drug Content	97.6 ± 2.1	98.1 ± 1.6
% Drug release after 12 hour	99.4 ± 3.8	99.2 ± 2.6

REFERENCES

1 Nayak A, Maji R, Das B, "Gastroretentive Drug Delivery System a review," *Asian Journal of Pharm Clin Res*., **2010**, 3(1), 2-10.

2 Goyal M, Prajapati R, Purohit KK, Mehta S, "Floating Drug Delivery System", *Journal of Current Pharmaceutical Research*, **2011**, 5(1),7- 18.

3 Sunil Kumar, Faraz jamil, "Gastro Retentive Drug Delivery System: Features and Facts" *International Journal of Research in Pharmaceutical and Biomedical Sciences*, **2012**, 3 (1), 125 -136.

4 Jamil F, Sunil K, Sharma S, Vishvakarma P, Singh L, "Review on Stomach Specific Drug Delivery Development and Evaluation", *IJRPBS*, **2011**, 2(4), 1427- 1433.

5 Vishal Bhardwaj, Nirmala, S.L. Harikumar, "Floating Drug Delivery System: a review", *Pharmacophore,* **2013**, 4 (1), 26-38.

6 Devkant Sharma, Anjali Sharma, "Gastroretentive Drug Delivery System - a mini review", *Asian pacific Journal of Health Sciences*, **2014**, 1(2), 80-89.

7 Vedha Hari, "The Recent Developments on Gastric Floating Drug Delivery Systems: An Overview", *Int Journal pharmtech Res*.**2010**, 2(1), 524-534.

8 Gopalakrishnan S, Chenthilnathan A., "Floating drug delivery systems: a review." *J Pharm Sci Technol,* **2011**, 3, 548–554.

9 Klausner EA, Lavy E, Friedman M, "Expandable gastroretentive dosage forms." *J Control Release*, **2003**, 90, 143– 162.

10 Narang N. "An updated review on: floating drug delivery system (FDDS)." *Int J App Pharm*, **2011**, 3, 1–7.

11 Peptic Ulcer, Disease Information, Sep 2018: - https://www.healthline.com/health/peptic-ulcer.

12 Drug Information, Sep 2018:- https://www.drugbank.ca/drugs/DB12770.

13 Drug Information, Sep 2018:- https://www.rxlist.com/Lafutidine.html

14 Drug Information, Sep 2018:- https://pubchem.ncbi.nlm.nih.gov/compound/Lafutidine

15 Drug Information, Sep 2018:- https://www.drugs.com

16 Raymond C, Paul J, Marian E, Handbook of Pharamaceutical excipients, sixth edition, 2009.