ORIGINAL RESEARCH

ISSN (O): 2349-5332
CODEN: IRJPHY

"FORMULATION AND EVALUATION OF BILAYER TABLET OF AMOXICILLIN TRIHYDRATE AND FAMOTIDINE HCL BY USING DIRECT COMPRESSION METHOD"

Samiksha P. Kotkar, Kalpeshkumar S. Wagh

Department of Pharmaceutics, Kisan Vidya Prasarak Santha's Institute of Pharmaceutical Education, Boradi, Dhule-425428.

Submitted on: 03.06.2024; **Revised on:** 09.06.2024; **Accepted on:** 11.06.2024

ABSTRACT:

Objective: This research focused on designing a novel gastro retentive bilayer drug delivery system combining Amoxicillin Trihydrate and Famotidine Hydrochloride to treat Helicobacter pylori-associated peptic ulcers. The goal was to mitigate side effects, extend the duration of action, and reduce the frequency of drug administration, ultimately enhancing patient outcomes. Bilayer gastric retentive floating tablets (BGRFT) with Famotidine HCl and Amoxicillin Trihydrate using HPMC K15M, HPMC K4M, CarbapolP940 and sodium bicarbonate have been developed to prolong the gastric residence time and increase drug bioavailability. Literature review revealed no published studies on the present study.

Materials and Method: The bilayer tablet features an immediate-release layer of Famotidine Hydrochloride and a gastro retentive layer of Amoxicillin Trihydrate, designed to optimize drug delivery. The gastro retentive layer is formulated with HPMC K15M and HPMC K4M as floating agents, sodium bicarbonate and citric acid as gas-generating agents, and Crospovidone as a superdisintegrant for the immediate-release layer. The prepared gastro retentive layer was thoroughly evaluated for various parameters, including pre-compression characteristics, physical properties (hardness, friability, weight uniformity, and drug content uniformity), swelling index, in-vitro floating behaviour, and in-vitro drug release. A simultaneous estimation method was employed to quantify Famotidine Hydrochloride and Amoxicillin Trihydrate in the formulation.

Results: Optimized formulations were characterized by FTIR studies and found no interactions between drug and polymer. The immediate-release layer of Famotidine Hydrochloride exhibited a rapid release profile, with 94.3% ± 0.02% of the drug released within the initial 30 minutes. In contrast, the sustained-release floating layer of Amoxicillin Trihydrate showed a slower and more prolonged release pattern, with 64.3% ± 0.06% of the drug released over a period of 10 hours.

Conclusion: This research explores the development of a novel drug delivery system that combines immediate and extended-release formulations, aiming to enhance therapeutic outcomes and improve patient compliance. By integrating both release profiles, this innovative approach seeks to optimize drug efficacy and convenience, ultimately leading to better treatment experiences and health outcomes.

Key words: Amoxicillin Trihydrate, Bilayer floating tablets, Sodium bicarbonate, Famotidine Hydrochloride, Gastro retentive drug delivery system.

Corresponding author: Samiksha P. Kotkar
E-mail: kotkarsamiksha392@gmail.com

Indian Research Journal of Pharmacy and Science; 39(2024)3049-3072;
Journal Home Page: https://www.irjps.in

INTRODUCTION

The oral route of drug administration is the most popular choice among healthcare professionals and pharmaceutical manufacturers, owing to its high patient acceptability. Solid dosage forms, particularly tablets, dominate the market, accounting for around 50-60% of all available formulations. These controlled-release systems are distinguished by a characteristic drug release pattern, where the drug concentration remains within the therapeutic range for a prolonged duration, ensuring continuous therapeutic efficacy.[1]

Peptic ulcers are characterized as open sores in the gastrointestinal tract, specifically in the stomach or duodenum. The two primary types of peptic ulcers are gastric ulcers and duodenal ulcers. The development of peptic ulcers occurs due to an imbalance between the aggressive factors (such as acid, pepsin, bile, and Helicobacter pylori) and the defensive factors (including gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, and the intrinsic resilience of mucosal cells).[2]

Effective treatment for Helicobacter pylori eradication is challenging, necessitating a combination of antibiotics and gastric acid inhibitors. To overcome the limitations of conventional therapy and enhance the efficacy of drug regimens, a well-designed drug delivery system is crucial. Gastro retentive drug delivery systems offer a solution by retaining the drug in the stomach, prolonging contact with the absorbing membrane, and increasing efficacy. This is particularly important for treating microorganisms that colonize the stomach, as gastric emptying, acidity, and the epithelial mucus layer can significantly reduce drug delivery to these areas.

Amoxicillin, a β-lactam antibiotic, operates through a shared bactericidal mechanism with other members of its class. International guidelines recommend amoxicillin as a primary treatment option for Helicobacter pylori infections.[3]

Famotidine acts as a histamine H2-receptor antagonist, exerting its effects through competitive inhibition of histamine H2-receptors on parietal cell membranes, thereby reducing gastric acid secretion. The current study aims to formulate and characterize immediate-release famotidine tablets using synthetic superdisintegrants like crospovidone, optimizing their properties for enhanced therapeutic outcomes.[4-5]

This study focuses on the development of gastro retentive bilayer floating tablets with tailored release profiles for amoxicillin and ranitidine. Amoxicillin Trihydrate, an antibiotic effective against H. pylori, and famotidine hydrochloride, an antacid that reduces gastric acid secretion, are combined in a novel formulation designed to optimize their complementary therapeutic effects. By creating a bilayer floating tablet with distinct release patterns for each drug, this innovative approach aims to enhance treatment outcomes for patients with H. pylori infections and associated gastric acid disorders.

MATERIALS AND METHOD

MATERIALS:

The present study received amoxicillin trihydrate and famotidine as gift samples from Gujrat Lyka Organics Ltd., Ankaleshwar, India, and Niksan Pharmaceuticals, Ankaleshwar, India, respectively. HPMC K4M and HPMC K15M were sourced from Powder Pack Chem Pvt. Ltd., Mumbai, while Ponceau 4R was obtained from Koel Colours Private Limited. Citric acid and sodium bicarbonate were purchased from Suvchem Laboratory Chemicals, and lactose monohydrate and magnesium stearate were acquired from Loba Chemie Pvt. Ltd., Mumbai. All other chemicals used were of analytical grade.

METHODS:

Preparation of Gastro retentive Bilayer tablet:

The development of gastro retentive bilayer tablets involved a two-stage process:[6]

i. Formulation of the immediate-release layer containing Famotidine hydrochloride, which served as the top layer.
ii. Formulation of the sustained-release layer containing Amoxicillin Trihydrate, which formed the bottom floating layer.

I. Preparation of Famotidine Hydrochloride Immediate Release Layer

The immediate-release layer of Famotidine hydrochloride was formulated using a direct compression method, with varying concentrations of crospovidone and microcrystalline cellulose at three different levels. The active ingredient, Famotidine hydrochloride, was accurately weighed and sieved through a mesh no. 40 to ensure uniform particle size. Meanwhile, crospovidone, microcrystalline cellulose, and lactose were sieved through a mesh no. 60 to create a homogeneous mixture. The ingredients were then blended in a poly bag for 5 minutes to ensure uniform distribution. Magnesium stearate, previously sieved through mesh no. 60, was added to the blend and mixed for an additional 3 minutes to enhance compressibility. Finally, the blend was compressed into tablets using a single punch tablet compression machine. The composition of FAM tablet layer is shown in Table 1.

Table No.1: Composition of 150 mg Immediate Release Layer of Famotidine hydrochloride (all quantities are expressed in milligrams (mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Famotidine Hydrochloride	40	40	40	40	40	40	40	40	40
Crosspovidone	3	3	3	6	6	6	9	9	9
Microcrystalline cellulose	15	30	45	15	30	45	15	30	45
Lactose	84.5	69.5	54.5	81.5	66.5	51.5	71.5	63.5	48.5
Magnesium stearate	7.45	7.45	7.45	7.45	7.45	7.45	7.45	7.45	7.45
Ponceau4R	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Total	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

II. Preparation of Amoxicillin Trihydrate Sustained Release Layer

The sustained-release layers of Amoxicillin Trihydrate were formulated using an experimental design approach, where the concentrations of HPMC K4M, HPMC K15M, and Carbopol P-940 were varied. The direct compression method was employed to prepare the layers. Amoxicillin Trihydrate was accurately weighed and sieved through a mesh no. 40 to ensure uniform particle size. Meanwhile, HPMC, Carbopol, sodium bicarbonate, citric acid, and lactose were sieved through a mesh no. 60 to create a homogeneous mixture. The ingredients were then blended in a poly bag for 5 minutes to ensure uniform distribution. Magnesium stearate, previously sieved

through mesh no. 60, was added to the blend and mixed for an additional 3 minutes to enhance compressibility. The blend was then compressed into tablets using a single punch tablet compression machine. The composition of the AMOX tablet layer is presented in Table 2.

TableNo.2:Compositionof450mgSustainedReleaseLayerofAmoxicillin Trihydrate (allquantities are expressed in milligrams (mg))

Ingredients	A1	A2	A3	A4	A5	A6	A7	A8	A9
Amoxicillin Trihydrate	250	250	250	250	250	250	250	250	250
HPMCK4M (10-30%)	45	90	135	0	0	0	0	0	0
HPMCK15M (10-30%)	0	0	0	45	90	135	0	0	0
CarbopolP940 (10-30%)	0	0	0	0	0	0	45	90	135
Sodium bicarbonate	36	36	36	36	36	36	36	36	36
Citricacid	9	9	9	9	9	9	9	9	9
Magnesium stearate	11.5	11.5	11.5	11.5	11.5	11.5	11.5	11.5	11.5
Total	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**

Fabrication of Gastro retentive Bilayer tablet

The immediate-release layer of Famotidine was placed on top of the sustained-release layer of Amoxicillin as the upper punch was raised, and the two layers were then compressed into a single floating bilayer tablet. Each tablet had a total weight of 600 mg, comprising 40 mg of Famotidine and 250 mg of Amoxicillin. A representation of the bilayer tablet, featuring Famotidine hydrochloride as the upper layer and Amoxicillin Trihydrate as the bottom layer, is depicted in Figure 1.Bilayer tablet of Amoxicillin Trihydrate & Famotidine HCl prepare through single press.

FigNo.1:Formulation ofbilayertablet

- **Pre-formulation Studies of powder blend:**[7]
- **Characterization of APIs:**

1. **Organoleptic Properties:** It includes tablets colour, presence or absence of an odor, taste, etc.

2. **Melting Point:** Melting point of drug was determined by capillary method.
3. **Solubility:** Take a small quantity of sample & add the solvent until the sample completely dissolves. It is examined visually for the presence of any undissolved particles.
4. **Spectral analysis of Amoxicillin Trihydrate and Famotidine hydrochloride:**

Preparation of 0.1N Hydrochloric acid:

Accurately measure 8.5ml of conc. Hydrochloride and sufficient water to make up to1000 ml.

➢ **Standard Calibration curve of Amoxicillin Trihydrate:**

Standard calibration curve of Amoxicillin Trihydrate was estimated by UV spectrophotometer in 0.1N HCl.

- **Preparation of stock solution:**

Accurately weigh 10 mg Amoxicillin Trihydrate and dissolved in 10 ml of 0.1N HCl in volumetric flask. Flask was shaken for 5 minutes to dissolve drug properly. Flask was labelled as Stock Solution.

- **Preparation of standard solution:**

Pipette out 1ml of stock solution & it was further diluted into 10ml of 0.1 N HCl. Then from the standard stock solution withdraw 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, and 1ml into five 10 ml different volumetric flasks. Then make up the volume to 10 ml with 0.1 N HCl to get 2, 4, 6, 8, 10 µg/ml concentration.

- **Determination of λ-max of Amoxicillin Trihydrate:**

The absorbance of each test solution was measured at λ_{max} i.e. **229 nm** of Amoxicillin Trihydrate in UV visible spectrophotometer against 0.1N HCl as blank solution.

➢ **Standard Calibration curve of Famotidine hydrochloride:**

Standard calibration curve of Famotidine hydrochloride was estimated by UV spectrophotometer in 0.1N HCl.

- **Preparation of stock solution:**

Accurately weigh 10 mg Famotidine hydrochloride and dissolved in 10 ml of 0.1N HCl in volumetric flask. Flask was shaken for 5 minutes to dissolve drug properly. Flask was labelled as Stock Solution.

- **Preparation of standard solution:**

Pipette out 1ml of stock solution & it was further diluted into 10 ml of 0.1 N HCl. Then from the standard stock solution withdraw 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, and 1 ml into five 10 ml different volumetric flasks. Then make up the volume to 10 ml with 0.1N HCl to get 2, 4, 6, 8, 10 µg/ml concentration.

- **Determination of λ-max of Famotidine hydrochloride:**

The absorbance of each test solution was measured at λ_{max} i.e. **266 nm** of **Famotidine hydrochloride** in UV visible spectrophotometer against 0.1NHClas a blank solution.

5. **Drug-Excipient Compatibility study by FT-IR:**

- **Procedure-** The KBr disk sample preparation technique (pressed pellet technique) was used to obtain the IR spectra of the samples on an IR spectrophotometer. The infrared spectra of pure drugs and all formulations were recorded by using a Fourier transform infrared spectrophotometer (SHIMADZU FTIR). A base line correction was made using dried potassium bromide and then the spectrum of the pure drug. Weighed amount of drug (3mg) was mixed with100 mg of potassium

bromide (dried at 40 - 50°C.

6. DSC analysis:

The DSC thermo gram of the drug showed a sharp endothermic peak, corresponding to the melting point of the drug.

- **Pre-compression studies of powder blend:**[8]

The prepared powder blend was evaluated for parameters like bulk density, tapped density, Carr's index, Angle of repose, and Hausner's ratio.

- **Post compression parameters:**

1. Physical appearance: [9]

It includes tablets size, shape, colour, presence or absence of an odor, taste, surface texture etc.

2. Weight variation:[10]

20 tablets were selected and weighed accurately. Acceptance criteria average weight of tablets was fixed at 600 mg

3. Tablet hardness:[11]

- **Apparatus:** Monsanto Hardness Tester
- **Procedure:** Five tablets were randomly selected. One tablet at a time was placed in the hardness tester which was already set to zero. Pressure was applied by pressing start button of the apparatus, till the tablet break. Reading on the tester i.e. the hardness of the tablets was noted down in Kg/sq cm.

4. Tablet thickness:[12]

Thickness was measured using Vernier Callipers.

5. Friability test:Apparatus:[13]

- **Apparatus:** Roche Friability test apparatus.
- **Procedure:** The apparatus consist of plastic chamber, which is divided into two parts and it revolves at a speed of 25 r.p.m. 20 tablets are weighed and placed in the plastic chamber. The chamber is rotated for 4 minutes or 100 revolutions. During each revolution the tablets falls from the distance of 6 inch. The tablets are removed from the chamber after 100 revolutions and weighed. Loss in weight indicates the friability. The tablets are considered to be of good quality if the loss in weight is less than 0.8%.

$$F=(1-W/Wo)100$$

Where,

Wo- Weight of tablet before test.

W- Weight of tablet after test.

6. Swelling index:[14]

Placing the tablet in the USP Dissolution Testing Apparatus II, in 900 ml of 0.1 N HCl at37 ± 0.5 °C, rotated at 50 rpm for 30 minutes. The tablets were removed from dissolution medium, blotted to remove excess water and weighed. Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation.

$$\text{Swelling Index}=(W_t-W_o)*100/W$$

Where,

W_t=Weight of dry tablet,

W_O= Weight of swollen tablet

7. Floating lag time:[15]

It floating lag time the tablet constantly floats on the dissolution medium (i.e. duration of floating) in the dissolution medium. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

8. Total floating time:[16]

A glass beaker containing 100 ml of 0.1N HCl was taken, in which bilayer tablet (Amoxicillin Trihydrate tablet layer) was placed for observation. The total duration for which tablet remains floating was recorded as duration of floatation.

9. In-Vitro Disintegration Test:

The process of breakdown of a tablet into smaller particles is called as disintegration. The in vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using 0.1 N HCl maintained at 37± 2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the 0.1 N HCl maintained at 37 ± 2 °C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

10. In-Vitro Drug release:[17]

In vitro drug release was performed according to the USP dissolution apparatus II (paddle) at 100 rpm and 37±0.5˚c temperature over a 10 hrs period for Amoxicillin Trihydrate SR and 1 hrs for Famotidine hydrochloride IR, using an automated paddle dissolution system. The media used was0.1NHCland volume of900 ml for the first 1 hr after then 0.1N HCl again maintained at 37±0.5˚c up to 10 hours for Amoxicillin Trihydrate SR and upto 30 mins for Famotidine hydrochloride IR. To maintain the sink condition, 5 ml samples were withdrawn at regular intervals and replaced with fresh dissolution media in the same volume and the concentration of dissolved drug was determined using U.V. spectrophotometer at λmax 229 nm and 266 nm for Amoxicillin Trihydrate and Famotidine hydrochloride.

11. Drug Content for Bi-layered tablet:

Ten tablets were weighed and average weight is calculated. All tablets were crushed and powder equivalent to 100mg drug was dissolved in 0.1N HCl and the volume was made upto100ml with 0.1N HCl. The solution was kept in sonicator for 1hr. From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with 0.1 N HCl. Solution was filtered and absorbance was measured spectro-photometrically at 229 nm Amoxicillin Trihydrate for and 266 nm for Famotidine hydrochloride against 0.1N HCl as blank. Amount of drug present in one tablet was calculated.

12. Stability studies:

Stability of a drug has been defined as the ability of a particular formulation in a specific condition, to remain within its physical, chemical, therapeutical and toxicological specifications. The reason of stability testing is to provide evidence on how the quality of drug formulation varies with time under the influence of various environmental conditions such as temperature, humidity, light. From this study we know about recommended storage condition, re-test periods and shelf-life of the drug can be established.

- **Storage conditions:**

The selected formulations were subjected for three month stability study as per ICH guidelines. The selected formulations were placed in a wide mouth glass bottles, mouth of the bottles were tightly closed and packed in aluminum foils. In the present study, stability studies were carried out at 25ºC / 60% and 40ºC / 75% RH for a specific period of 3 months for the selected formulations.

- **Purpose of stability studies:**

Stability studies are done to understand how to design a product and its packaging, such that product has appropriate physical, chemical and microbiological properties during a defined shelf life when stored and use

RESULT AND DISCUSSION:

- **Evaluation of tablet:**
- **Pre-formulation Study:**
- **Organoleptic Studies of API:**

Table No. 3: Organoleptic characteristics of API

Sr. No.	Organoleptic Analysis	Result (Amoxicillin Trihydrate)	Result (Famotidine hydrochloride)
1	**Colour / Appearance**	Paleyellow	White to Pale yellow
2	**Odour**	Characteristic odour	Unpleasant odour
3	**Taste**	Bitter	Bitter

- **Melting point determination:**

The melting point was carried out by using capillary tube method. Melting point of Amoxicillin Trihydrate and Famotidine hydrochloride was found to be in the range of 198°C and163°C

Table No. 4: Determination of melting point of A

Sr. No.	Melting Point		
	API	Observed value	Standard value
1	**Amoxicillin Trihydrate**	198°C	197-204°C
2	**Famotidine hydrochloride**	163°C	163-164°C

- **Solubility:**

Amoxicillin Trihydrate exhibits solubility in various solvents, including Distilled Water, Diluted Sodium Hydroxide (NaOH), Ethanol, and Methanol. On the other hand, Famotidine hydrochloride is soluble in Methanol, Distilled Water, and Glacial Acetic Acid, making it compatible with a range of solvents.

Table No 5: Solubility of Amoxicillin Trihydrate and Famotidine Hydrochloride

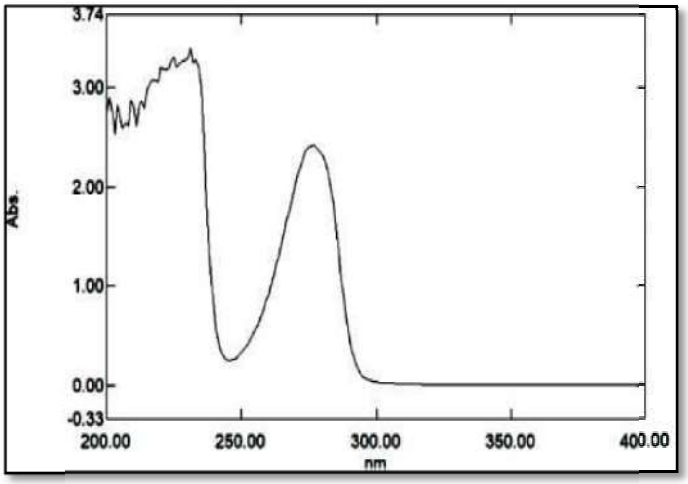
Amoxicillin Trihydrate		Famotidine Hydrochloride	
Solvent	**Solubility**	**Solvent**	**Solubility**
Dil. NaOH	Soluble	**Glacial acetic acid**	Freely Soluble
Distilled Water	Slightl ysoluble	**Distilled Water**	Very Slightly soluble
Ethanol	Slightl ysoluble	**Methanol**	Slightly soluble
Methanol	Slightl ysoluble	**Ethanol**	Insoluble

- **UV Visible Spectrophotometer analysis:**
- **Determination of λmax:**

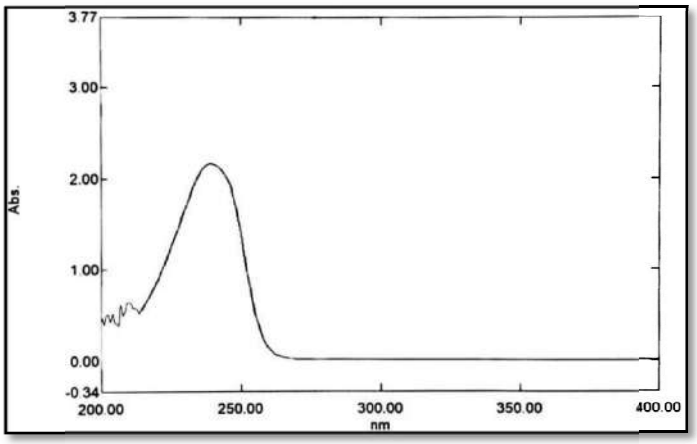
The absorption maxima (λmax) of Amoxicillin Trihydrate and Famotidine hydrochloride in 0.1 N HCl were determined using UV spectrophotometry. Based on these findings, it was concluded that the received samples of Amoxicillin Trihydrate and Famotidine hydrochloride were of high purity, making them suitable for use in the formulation of bilayer tablets.

Table No. 6: Wavelength maximum (λmax) of Amoxicillin Trihydrate and Famotidine hydrochloride

Drug	λmax	
	Actual λmax	Observed λmax
AmoxicillinTrihydrate	229nm	**229nm**
Famotidinehydrochloride	266nm	**266nm**



FigNo.2: λmax of Amoxicillin Trihydrate



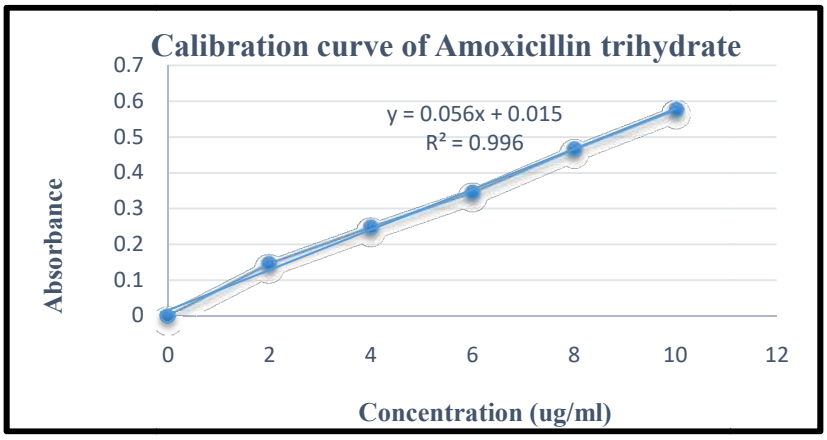
FigNo.3: λmax of Famotidine hydrochloride

- **Plot of calibration curve:**

A standard calibration curve for Amoxicillin Trihydrate was generated using UV spectrophotometry in 0.1 N HCl. This calibration curve will serve as a reference for subsequent quantification of Amoxicillin Trihydrate.

TableNo.7: Absorbance of Amoxicillin Trihydrate

Concentration (ug/ml)	Absorbance
0	0
2	0.146
4	0.248
6	0.345
8	0.466
10	0.576

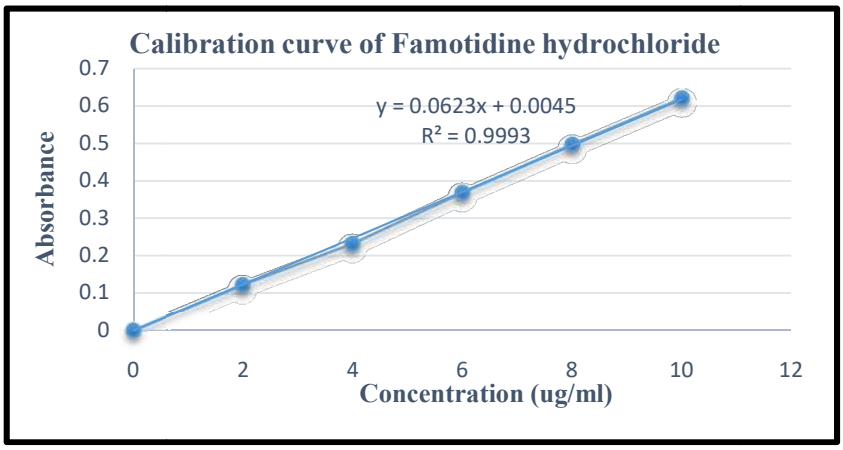


FigNo.4: Calibration curve of Amoxicillin Trihydrate

A standard calibration curve for Famotidine hydrochloride was established using UV spectrophotometry in 0.1 N HCl. The absorbance of the drug was measured across a concentration range of 2-10 µg/ml, and the results demonstrated a linear relationship, confirming compliance with Beer's Law. This calibration curve will serve as a reference for subsequent quantification of Famotidine hydrochloride.

TableNo.8:Absorbance of Famotidine hydrochloride

Concentration(ug/ml)	Absorbance
0	0
2	0.123
4	0.233
6	0.369
8	0.497
10	0.621



FigNo.5: Calibration curve of Famotidine hydrochloride

- **Drug compatibility study by FTIR Spectroscopy:**

The identity of the drug was confirmed through FTIR spectroscopy, which revealed a spectrum characteristic of Amoxicillin Trihydrate. The sample's FTIR spectrum exhibited distinct absorption peaks corresponding to the various functional groups present in the drug, providing a unique fingerprint that verified its identity.

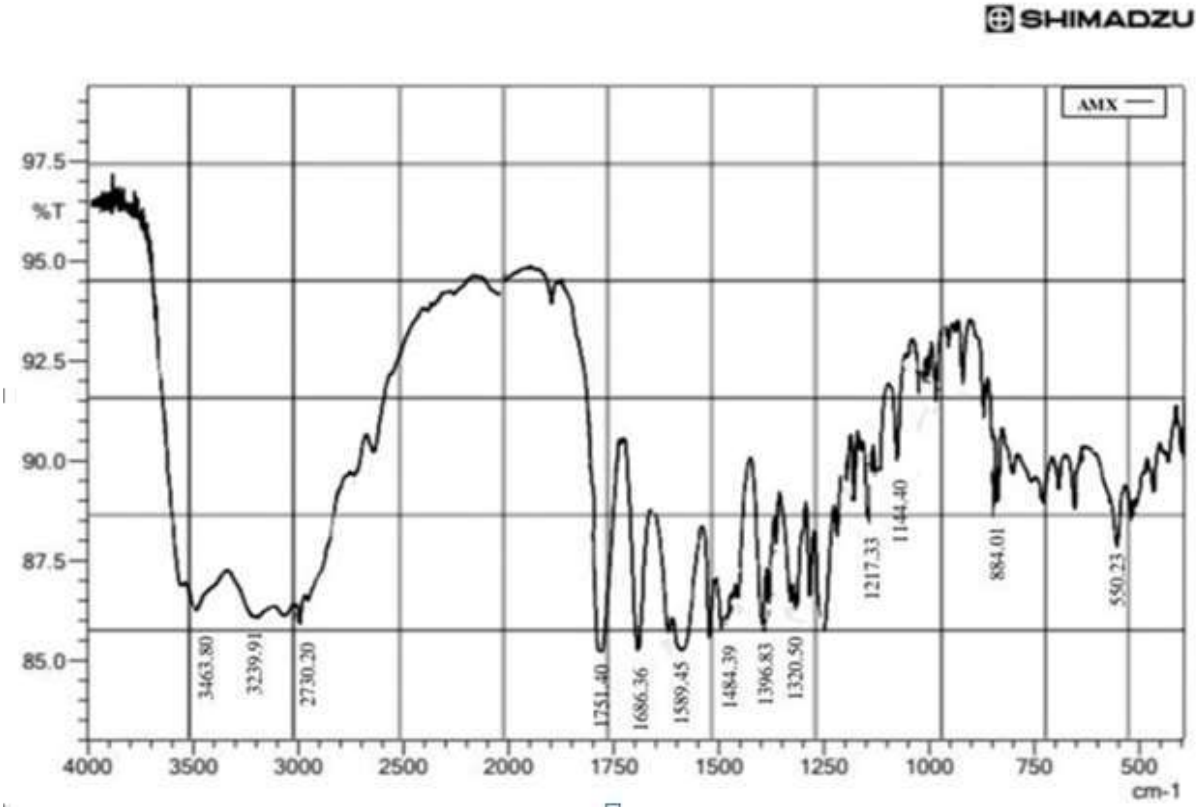
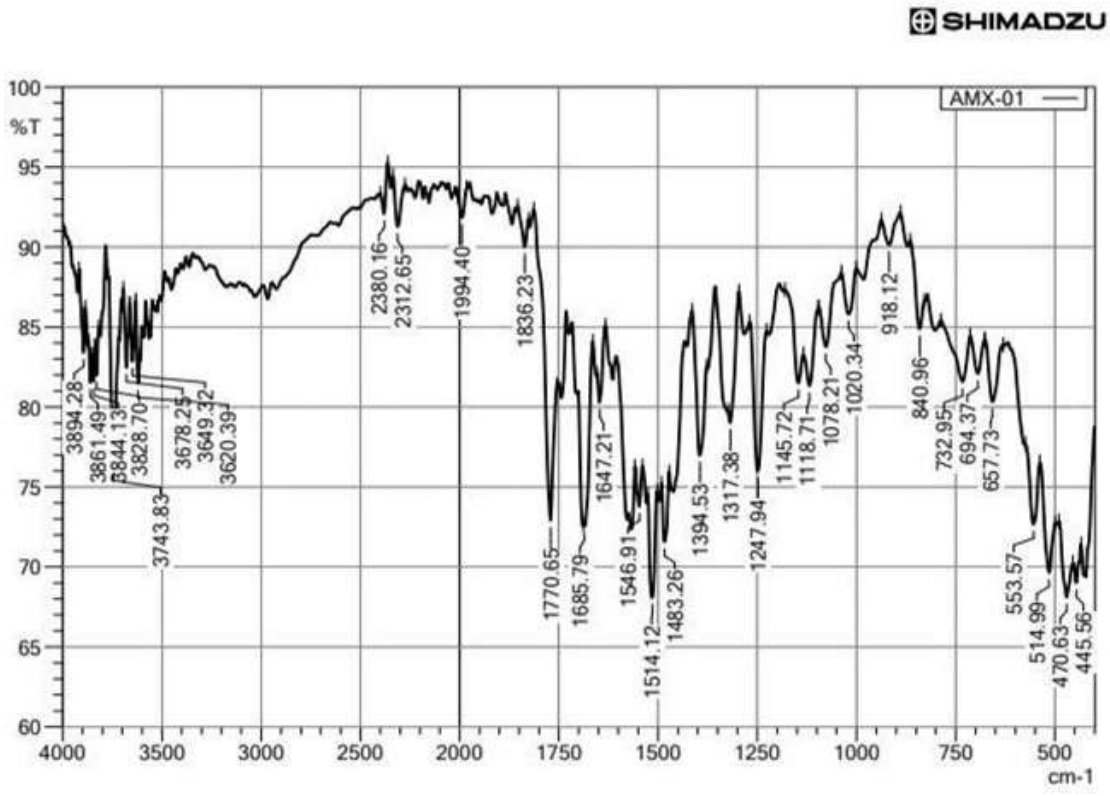
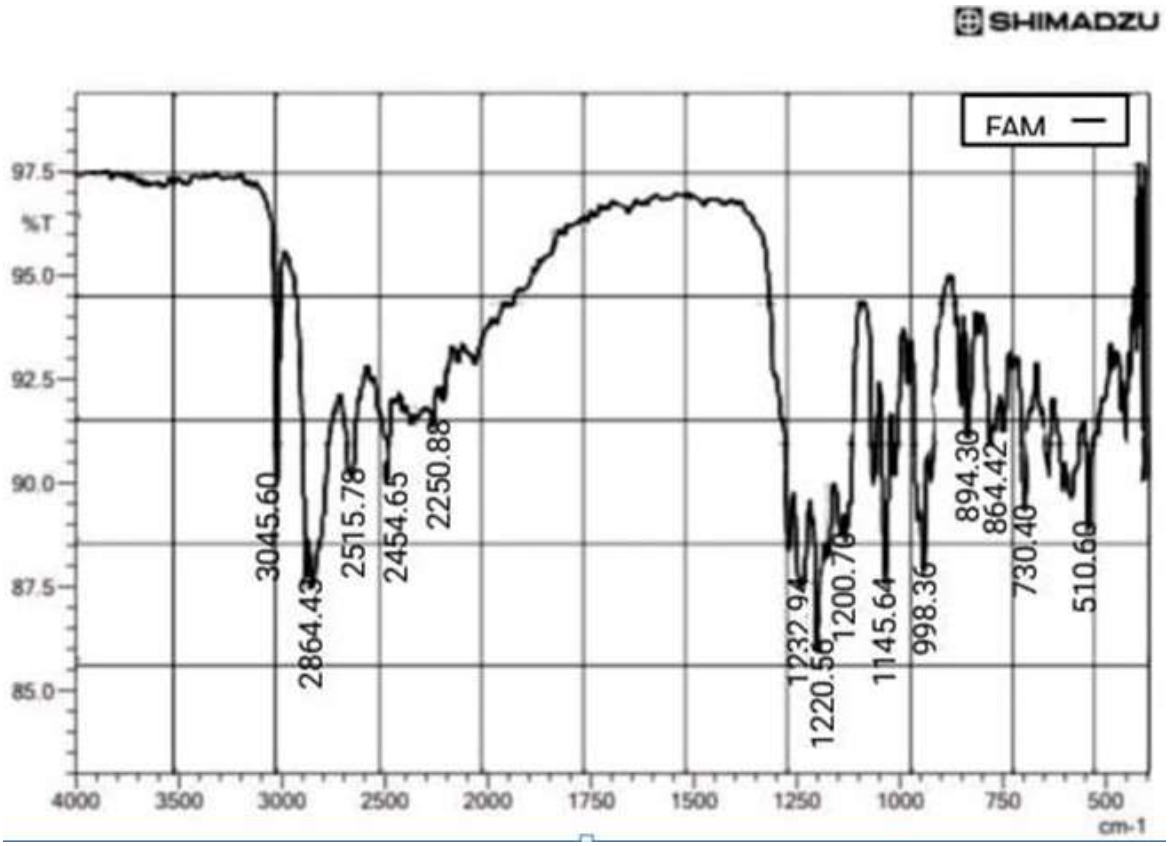


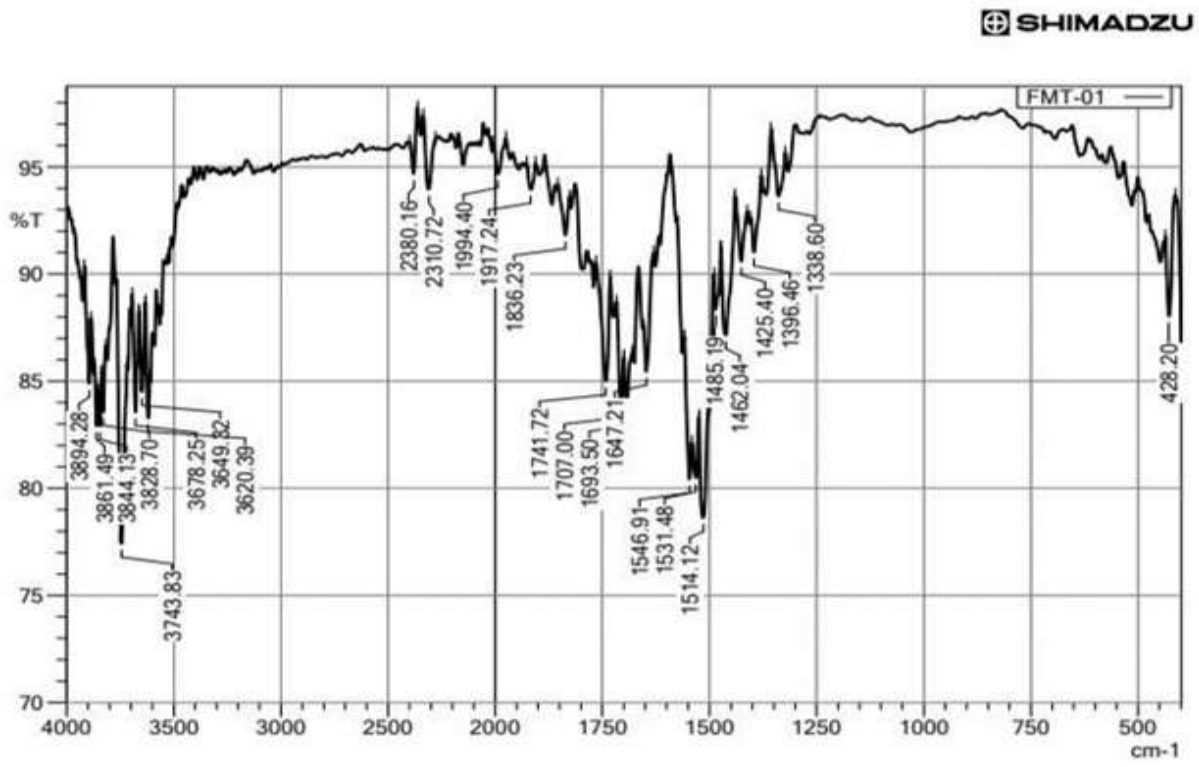
Fig No.6: FTIR spectrum of Amoxicillin Trihydrate



FigNo.7: FTIR spectrum of Amoxicillin Trihydrate + excipients



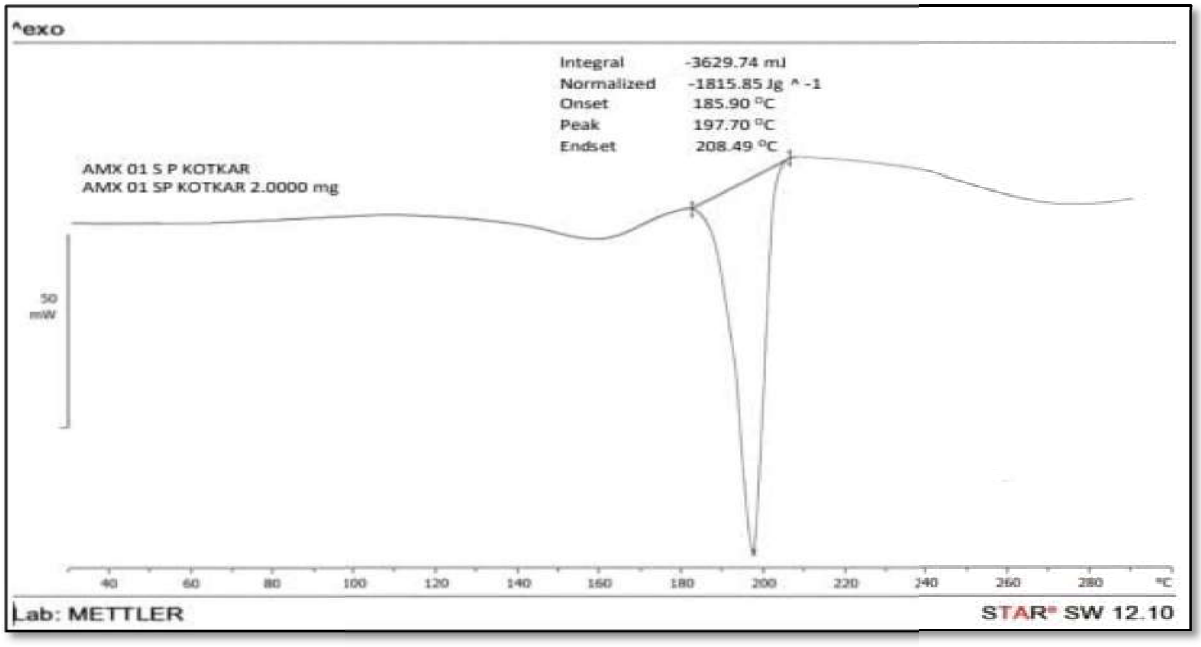
FigNo.8: FTIR spectrum of Famotidine hydrochloride



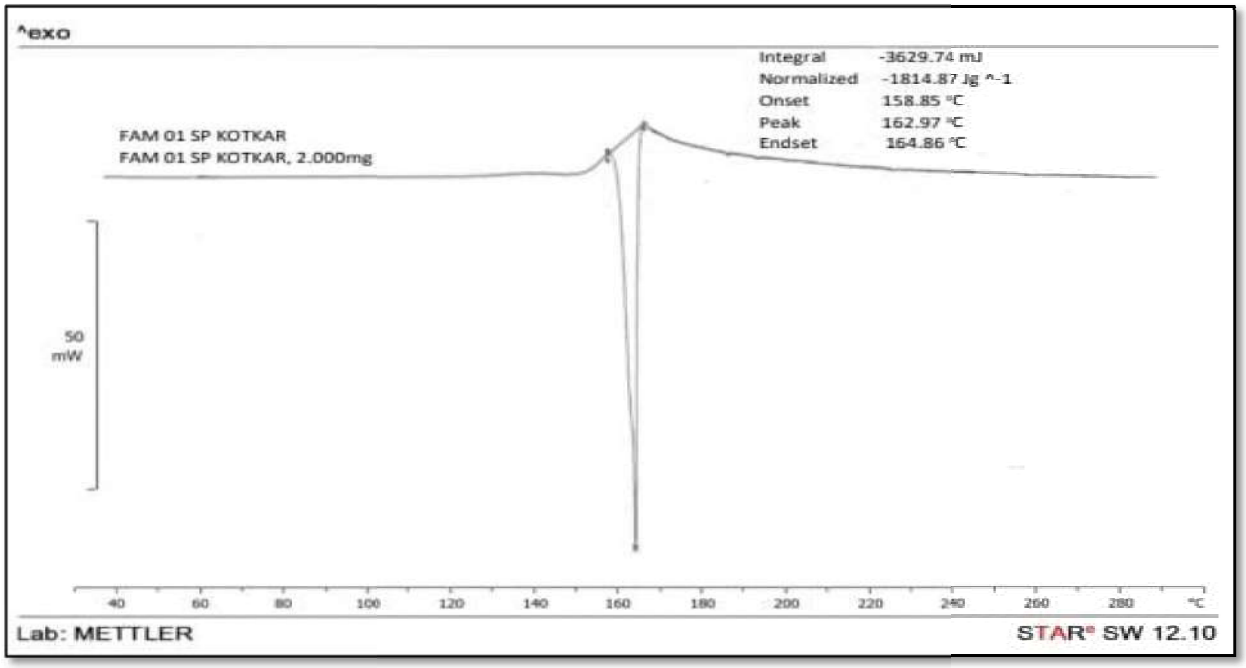
FigNo.9:FTIR spectrum of Famotidine hydrochloride + excipients

- **DSC Analysis:**

The resulting thermograms revealed distinct endothermic peaks at 197.70°C and 162.97°C, which correspond to the melting points of the respective drugs. These sharp peaks indicate the drugs' thermal transitions, providing insight into their thermal stability and purity.



FigNo.10:ThermalSpectraofAmoxicillin Trihydrate



FigNo.11:Thermal Spectra of Famotidine hydrochloride

- **Pre-compression parameters of powder blend:**

The prepared powder blend was evaluated for parameters like bulk density, tapped density, Carr's index, Angle of repose, and Hausner's ratio.

Table No.9 : Pre-compression parameters of powder blend prepared for Famotidine hydrochloride tablet layer

Batch	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner's ratio	Angle of repose(^{0})
F1	0.456±0.019	0.564±0.027	17.5±0.023	1.22±0.023	28.73±0.17
F2	0.456±0.030	0.568±0.024	19.8±0.020	1.25±0.027	26.19±0.17
F3	0.464±0.015	0.537±0.025	13.7±0.016	1.16±0.020	27.87±0.15
F4	0.456±0.015	0.584±0.024	22±0.015	1.26±0.019	28.55±0.14
F5	0.475±0.014	0.552±0.028	14±0.018	1.17±0.03	29.38±0.16
F6	0.479±0.020	0.558±0.024	14.2±0.019	1.17±0.022	28.69±0.18
F7	0.450±0.018	0.559±0.026	20±0.016	1.25±0.023	29.57±0.13
F8	**0.477±0.014**	**0.552±0.026**	**15.5±0.023**	**1.19±0.020**	**25.19±0.12**
F9	0.466±0.015	0.560±0.025	16.9±0.020	1.21±0.022	28.32 ±0.19

TableNo.10: Pre-compressionparametersofpowderblendpreparedforAmoxicillinTrihydratetabletlayer

Batch	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose(^{0})
A1	0.461±0.014	0.577±0.024	20.2±0.016	1.26±0.019	28±0.14
A2	0.458±0.018	0.578±0.027	20.8±0.012	1.27±0.022	27±0.14
A3	0.475±0.015	0.581±0.024	18.3±0.013	1.23±0.019	26±0.18
A4	0.466±0.013	0.584±0.024	20.3±0.018	1.26±0.018	28±0.16
A5	0.475±0.012	0.566±0.027	16.2±0.014	1.20±0.019	29±0.15
A6	0.482±0.016	0.567±0.022	15.2±0.015	1.18±0.019	26±0.13
A7	0.460±0.018	0.569±0.026	19.2±0.012	1.24±0.022	28±0.16
A8	**0.466±0.014**	**0.574±0.028**	**18.7±0.015**	**1.23±0.03**	**25 ± 0.17**
A9	0.472±0.015	0.580±0.023	18.7±0.013	1.23 ±0.019	29 ± 0.15

- **Post-compression parameters:**

- **Hardness:**

The hardness of the tablet layers was evaluated using a Monsanto hardness tester. To ensure accuracy, three tablets from each formulation were randomly selected and their hardness was determined. This testing protocol provided a reliable assessment of the tablets' mechanical strength.

- **Friability test:**

The friability of the tablets was assessed using a Roche friabilator. This weight loss indicates the tablets' susceptibility to abrasion and fragmentation. Notably, a weight loss of less than 0.5% to 1% is generally deemed acceptable, suggesting that the tablets exhibit adequate mechanical strength and resistance to degradation. The results indicate that the formulations meet the acceptable standards for friability

- **Uniformity of weight:**

The results showed a weight variation of 594.62mg ± 602.54mg, which falls within the acceptable limit of +/- 5% w/w. This suggests that the manufacturing process maintained a high level of precision and accuracy in terms of tablet weight.

- **Disintegration test:**

The time taken for complete disintegration, leaving no residue in the tube, was recorded.

- **Drug content:**

The results showed that the drug content in the Famotidine hydrochloride tablet layer ranged from 97.80% to 99.40%, while the drug content in the Amoxicillin trihydrate tablet layer ranged from 97.80% to 99.41%.

- **Floating parameters:**

- **Floating lag time:**

The floating lag time of the tablets was investigated at 37 ± 0.5°C in 100 ml of 0.1N HCl. A glass beaker containing 100 ml of 0.1N HCl was used to

observe the buoyancy of the AMOX tablet layer. The time taken for the tablet to float was visually monitored and recorded. The floating lag time for all formulations was determined in 0.1N HCl, and the values ranged from 40 ± 4 to 60 ± 5 seconds.

- **Total floating time:**

The duration of floatation was defined as the total time the tablet remained buoyant. To measure this, a bilayer tablet (Amoxicillin Trihydrate tablet layer) was placed in a glass beaker containing 50 ml of 0.1N HCl. The tablet's floating behavior was observed and recorded. This data provides insight into the tablet's ability to remain suspended in the gastric fluid, which is crucial for its therapeutic efficacy

(a) (b) (c)

Fig No.12: Floating time of bilayer tablet (a = Initial time; b = after 1 min; c = after 8 hrs)

- **Swelling index:**

The swelling behaviour of the AMOX-containing tablet layer was evaluated using the USP Dissolution Testing Apparatus II. The tablet was immersed in 900 ml of 0.1 N HCl at 37 ± 0.5 °C and rotated at 50 rpm for 30 minutes. After removal from the dissolution medium, the tablet was blotted to remove excess water and weighed.

TableNo.11:EvaluationparametersforAmoxicillin Trihydratetablet layer

Batch	Hardness(kg/cm^2)	Thickness(mm)	Friability(%)
B1	4.2±1.1	3.0±0.01	0.80
B2	4.6±1.3	3.0±0.02	0.89
B3	4.4±1.4	3.1±0.01	0.87
B4	4.3±1.8	3.2±0.01	0.90
B5	4.2±1.3	3.2±0.02	0.93
B6	4.3±1.1	3.3±0.01	0.89
B7	4.2±1.4	3.1±0.02	0.90
B8	**4.2±1.7**	**3.0±0.02**	**0.96**
B9	4.6±1.1	3.2±0.01	0.91

TableNo.12: Evaluation parameters for Famotidine HCl tablet layer

Batch	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
B1	4.2±1.1	3.0±0.01	0.560
B2	4.6±1.3	3.0±0.02	0.491
B3	4.4±1.4	3.1±0.01	0.663
B4	4.3±1.8	3.2±0.01	0.452
B5	4.2±1.3	3.2±0.02	0.565
B6	4.3±1.1	3.3±0.01	0.587
B7	4.2±1.4	3.1±0.02	0.482
B8	**4.2±1.7**	**3.0±0.02**	**0.561**
B9	4.6±1.1	3.2±0.01	0.466

TableNo.13:Evaluation parameters for Bilayer tablet

Batch	Weight uniformity (mg)
B1	598.10
B2	599.10
B3	600.04
B4	596.34
B5	589.23
B6	590.50
B7	602.54
B8	**599.62**
B9	596.31

TableNo.14: Evaluation parameters for Famotidine tablet layer

Batch	Drug content (%) (Famotidine hydrochloride)	Disintegration time (mins)
F1	98.56	1.5
F2	97.80	1.4
F3	99.65	1.2
F4	98.95	1.3
F5	98.87	1.2
F6	99.45	1.1
F7	98.39	1.5
F8	**99.40**	**1.3**
F9	98.90	1.3

TableNo.15: Evaluation parameters for Amoxicillin Trihydrate tablet layer

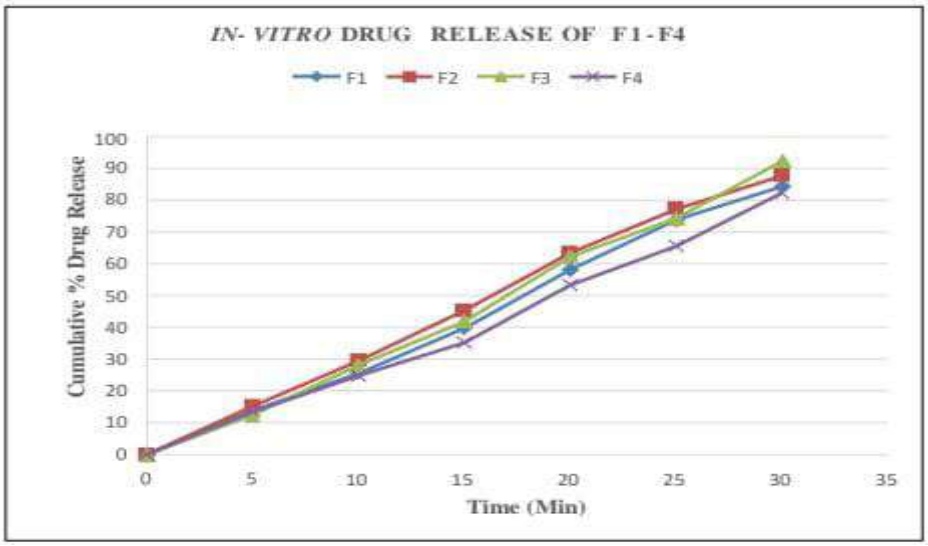
Batch	Drug content(%) (Amoxicillin Trihydrate)	Floating lag time (Mins)	Total Floating time (Hrs)	Swelling index
A1	98.66	1.12	7	12.2
A2	97.80	1.36	7.5	12.6
A3	99.35	1.45	8	12.7
A4	98.75	1.28	7	12.3
A5	98.97	1.44	7.5	12.8
A6	99.40	1.47	8	13
A7	98.29	1.38	7	12.4
A8	**99.40**	**1.46**	**8**	**12.8**
A9	98.90	1.43	7.5	12.5

- **In-vitro dissolution studies:**

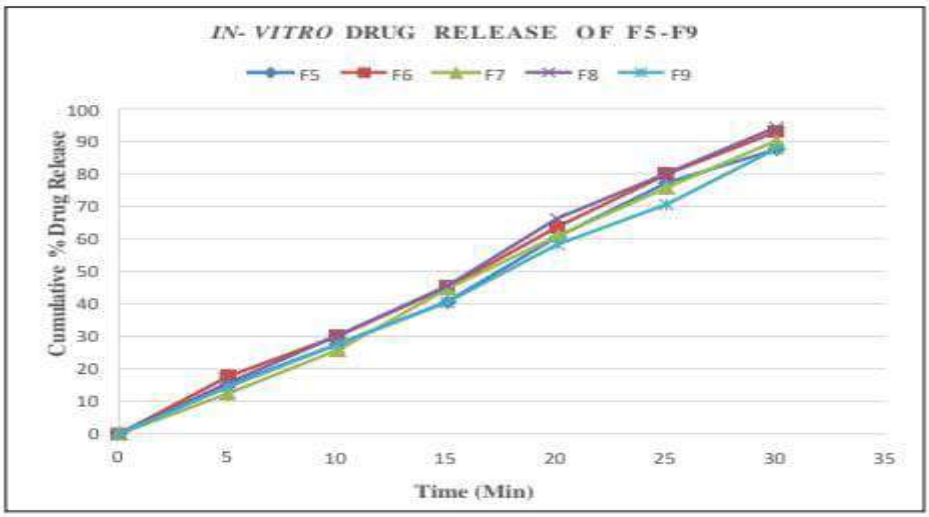
The in vitro dissolution profile of Famotidine hydrochloride tablet layers was investigated in 0.1N HCl buffer solution under sink conditions for a period of 30 minutes. The results revealed that the in vitro drug release for formulations F1 to F9, which were prepared using the direct compression technique, ranged from 12.5% to 94.3%. This indicates that the formulations exhibited varying degrees of drug release, with some formulations achieving nearly complete release and others showing more limited release. These findings provide valuable insights into the performance of these formulations under simulated gastric conditions.

Table No.16:*Invitro* drug release for all the formulations of Famotidine hydrochloride tablet layer

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	**0**	0
5	12.5	13.8	15.2	13.5	15.1	17.7	12.5	**15.8**	14.6
10	25.6	29.5	28.1	24.8	27.6	30.1	25.8	**30.2**	27.7
15	39.7	45.3	41.8	35.2	40.7	45.2	44.8	**45.6**	40.6
20	58.2	63.5	62.3	53.3	60.6	63.6	60.9	**66.2**	58.3
25	73.8	77.2	74.3	65.6	77.2	79.9	75.7	**80.1**	70.6
30	84.3	87.7	92.3	82.3	87.5	92.9	90.2	**94.3**	87.7



FigNo.13: In-vitro drug release of F1-F4



FigNo.14:In-vitrodrugreleaseofF5-F9

TableNo.17:*In-vitro* drug release for all the formulations of Amoxicillin Trihydrate tablet layer

Time(hrs)	A1	A2	A3	A4	A5	A6	A7	A8	A9
0	0	0	0	0	0	0	0	**0**	0
1	8.3	10.3	12.6	11.5	12.4	11.8	9.2	**8.7**	8
2	16.5	18.2	20.5	18.9	18.8	18	13.5	**14.5**	14.6
3	21.2	23.8	26.3	24.6	26.5	26	19	**20.4**	20

4	29.3	31.5	33.8	32.2	32.8	32	24.3	**27**	26
5	35.6	38.6	40.2	39.3	40.9	39.9	31.6	**32.9**	33.7
6	41.8	43.3	46.5	45.1	47.2	47.5	38.8	**38**	38.3
7	48.1	50.7	53.2	51.6	53.3	54.2	44.4	**45.3**	46
8	56.2	59.6	61.2	58.8	59.2	60.6	51.3	**51.8**	52.2
9	62.6	65.5	67.8	65.9	66.3	67.2	57.6	**59**	58.5
10	70.2	72.2	75.1	73	74.6	75.3	63.5	**64.3**	64.6

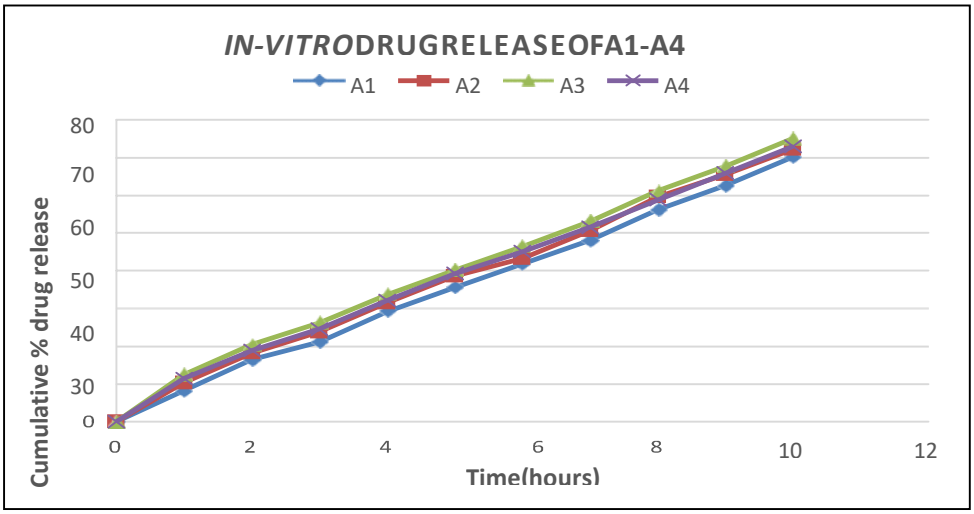
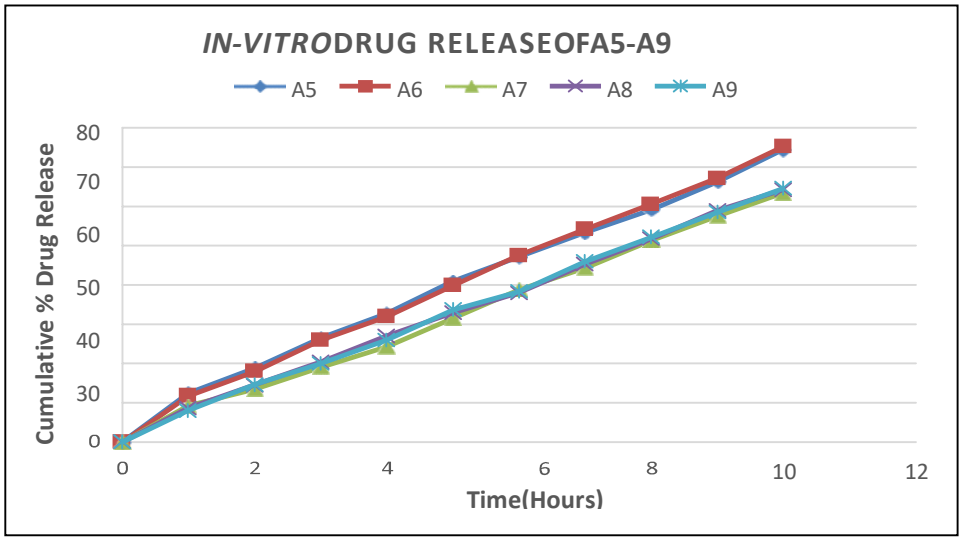


Fig No. 15: In-vitrodrugreleaseofA1-A4



FigNo.16:In-vitrodrugreleaseofA5-A9

- **Stabilitystudy(B8):**

The batch B8 has shown best results among the all formulations hence, it has selectedforstability study.The optimized sustained releaseformulation was subjected tostabilitystudies at40°C±2°C /75%RH±5%for3months.

Theproductwasevaluatedforfollowingparameters:

- Weight variation
- Hardness
- Friability
- Drugcontent
- Dissolutionanalysis

Storage condition at 40^0 C ± 2°C / 75%

TableNo.18: Stability data

Test	0 days	30days	60 days	90 days
Weight variation (mg)	599.62	599.62	598.15	598.12
Hardness (kg/cm^2)	4.2	4.2	4.1	4.1
Friability	0.561	0.561	0.560	0.560
Drug content (%)	99.40	99.40	99.29	99.25

The optimized formulation B8 was subjected to accelerated stability testing to assess its stability under stressful conditions. The study involved monitoring various parameters at regular intervals of 0, 30, 60 and 90 days. The results demonstrated that the optimized formulation remained stable and retained its properties throughout the study period, indicating its robustness under accelerated conditions. This outcome suggests that the formulation is likely to remain stable during its shelf life, ensuring its efficacy and safety for consumption.

Table No.19: Dissolution data of percentage cumulative drug release for formulation B8 (Famotidine hydrochloride tablet layer F8)

Time (mins)	0days	30days	60days	90days
0	0	0	0	0
5	15.8	15.7	15.6	15.5
10	30.2	30.2	30.2	30.1
15	45.6	45.5	45.4	45.2
20	66.2	66.2	66.2	66.1
25	80.1	80.1	79.9	79.8
30	94.3	94.3	94.2	94.1

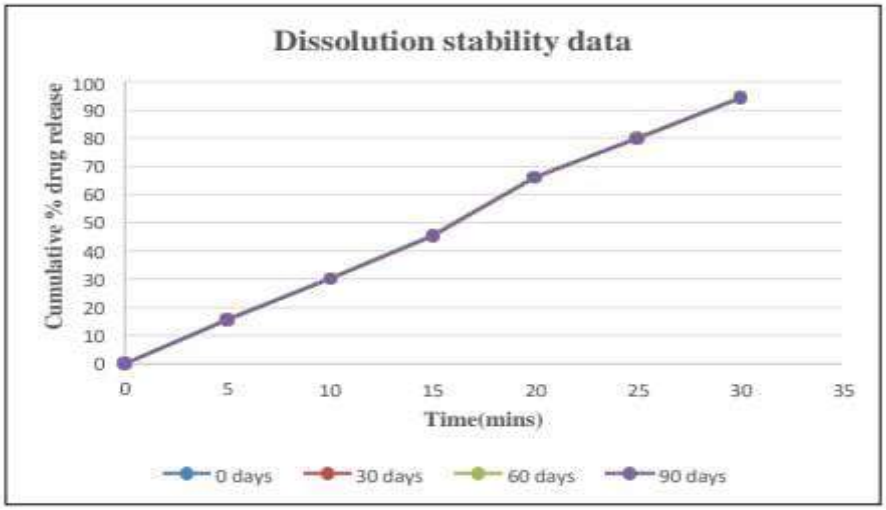


Fig No.17: Dissolution stability data for formulation B8 (Famotidine hydrochloride tablet layer)

Table No. 20 : Dissolution data of percentage cumulative drug release for formulation B8 (Amoxicillin Trihydrate tablet layer A8)

Time(hrs)	0 days	30days	60days	90days
0	0	0	0	0
1	8.7	8.6	8.5	8.4
2	14.5	14.4	14.3	14.1
3	20.4	20.3	20.2	20.0
4	27	26.9	26.7	26.6
5	32.9	32.8	32.6	32.5
6	38	37.9	37.7	37.5
7	45.3	45.3	45.2	45.0
8	51.8	51.7	51.5	51.3
9	59	58.9	58.7	58.5
10	64.3	64.3	64.2	64.1

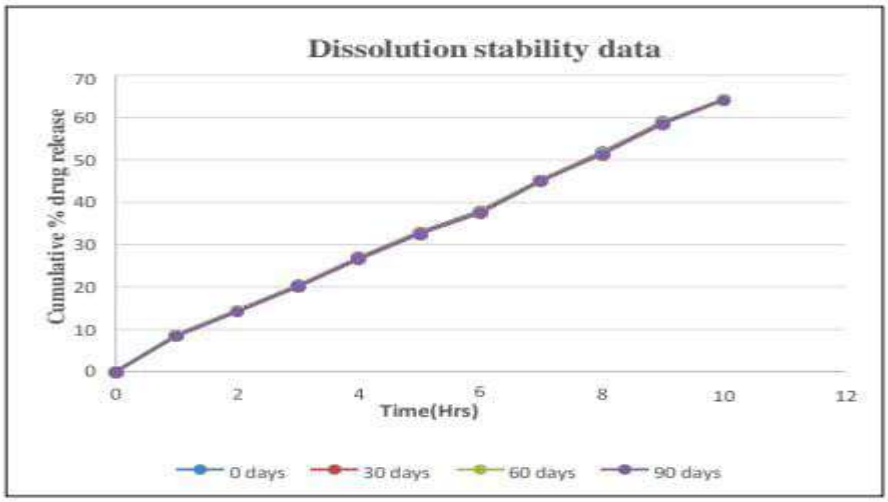


Fig No.18: Dissolution stability data for formulation B8 (Amoxicillin Trihydrate tablet layer)

CONCLUSION:

A novel gastro retentive delivery system was developed in the form of bilayer tablets, combining Famotidine Hydrochloride and Amoxicillin Trihydrate. The tablet features a rapid-release layer of Famotidine Hydrochloride and a sustained-release layer of Amoxicillin Trihydrate, designed to enhance therapeutic efficacy and patient convenience.

B8 batch is an optimum formulation and passes all physiochemical tests Based on evaluation parameters, such as high drug content and floating lag time, total floating time it was indicated that the B8 formulation batch was an optimum batch. The results are clearly indicating that Floating lag time and total floating time increases by increasing polymer concentration and disintegration time increases by increasing superdisintegrant concentration.Sodium bicarbonate added to keep the tablet weight constant on floating lag time and total floating time and hence used in the formulation of the floating tablets for keeping the tablet weight constant.

F8 formulation showed significant drug release, with 90 % of Famotidine hydrochloride released from the bilayer tablet. The dissolution profile of F8 formulation of bilayer tablets containing Famotidine hydrochloride demonstrates immediate release of the drug over a period of 30 mins, with the majority of the drug released between 25-30 mins. F8 formulation showed significant drug release, with 90 % of Amoxicillin Trihydrate released from the bilayer tablet. The dissolution profile of F8 formulation of bilayer tablets containing

Amoxicillin Trihydrate demonstrates sustained release of the drug over a period of 10 hrs, with the majority of the drug released between 8-10 hrs. This suggests that A8 formulation may be suitable for once-daily dosing regimens, providing immediate release of Amoxicillin Trihydrate and potentially improving patient compliance and therapeutic outcomes.Famotidine HCl immediate release tablet layer were rapidly disintegrate and dissolved to release the medicaments. Amoxicillin trihydrate sustained release tablet layer were effervescent gastric floating tablet layer were retained in the stomach for longer periods during fed state and released the drug in a controlled manner.

The stability study showed that no significant changes in tablets after 3 months study.

REFERENCES:

1. Joseph RR., Rhodes CT. Modern Pharmaceutics. 3rd edition, Marcel Dekker, Inc., New York. 1996; 58.
2. Tripathi KD. Essential of Medical Pharmacology. 6th Edition, Jaypee Brother Medical Publishers (P) Ltd.; 2008. 628.
3. F.Wangetal.Helicobacterpylori-inducedgastricinflammationandgastriccancer. CancerLett(2014):196-202.
4. Rose R S, Shanmu ganathan TRS, Senthil KSR, Thanga TA. Formulation andevaluation of mouth dissolving famotidine tablet. Int J Chem Tech Res 2009;1:1251-6.
5. Venkateswarlu B, Pragati BK, Debjit B. Formulation and evaluation of famotidinefastdissolvingtabletsbydirectcompr essionmethod.IndianJResPharmBiotechnolog y2013;1:609-13.
6. Shikha Jain, vikas Jain, S.C. Mahajan. Design and characterization of gastro retentive bilayer tablet of Amoxicillin Trihydrate and ranitidine hydrochloride forH. pylori infection. Indian Journal of

Pharmaceutical Education and Research Vol48, Oct-Dec, 2014:118-120.

7. Reddy Pradeep, Rao Divya, RaviKumar Bi-Layer Technology- AnEmerging Trend:AReview. InternationalJ ofResearch Development in Pharma Life Sci, 2013 April-May, Vol. 2, No.3.
8. Liberman H, Lachman L. The Theory and Practice of Industrial Pharmacy. 3rd ed.Bombay: Verghese Publication House; 1991 p. 171-193.
9. Martin A, Micromeritics. In: Martin A, ed. Physical Pharmacy. Baltimore's, MD:Lippincott Williams and Wilkins; 2001. p. 423-454.
10. D. Bhowmik, B. Chiranjib, Krishnakanth, Pankaj, R. Margret Chandira, FastDissolving Tablet: An Overview. Journal of Chemical and PharmaceuticalResearch. 2009; 1(1):163-77.
11. R Garg*, GD Gupta, Progress in controlled gastro retentive delivery systems,Tropical Journal of Pharmaceutical Research, September 2008; 7 (3): 1055-1066.
12. Martin A, Micromeretics. In: Martin A, ed. Physical Pharmacy. Baltimores, MD:Lippincott Williams and Wilkins; 2001:420-450.
13. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrialpharmacy. Philadelphia: Lea & Febiger; 1976.
14. Hansiya Sultana H, GB Kiran Kumar, Acharya A, Ahmed MG. Development andevaluation of chitosan based oral controlled release matrix tablets of Pregabalin.World J Pharm Pharma Sci. 2015; 4(6):1306-19.
15. Desai S, Bolton S, A Floating controlled release system: In-vitro – in-vivoevaluation, pharm. Res. 1993; 10:1321-1325.
16. Patel, V.F., Patel N.M., Yeole, PG., Studies on formulation and evaluation ofranitidine floating tablets; Ind. J. Pharm. Sci., 2005,67(6), 703-709.
17. Shibu B.S, Suresh S, Saravanan C. Formulation and Evaluation of ExtendedRelease Tablet of Divalproex Sodium using Different Polymers as ReleaseRetarding Agent. Int J Pharma Devel Tech. 2014; 4(3):145-50.

CONFLICT OF INTEREST REPORTED: NIL; SOURCE OF FUNDING: NONE REPORTED