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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLETS OF AMOXICILLIN TRIHYDRATE

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ABSTRACT

The aim of the present study was to formulate and evaluate gastroretentive floating tablets of Amoxicillin trihydrate, to provide local action in the treatment of Helicobacter pylori by prolonging the gastric residence time. The sustained release of Amoxicillin trihydrate is desired because of its short biological half-life (1-1.5hr) and bioavailability (60%). The gastro retentive floating tablets of Amoxicillin trihydrate will provide site-specific drug delivery and thereby extend its duration of action. The dosage form was designed by using HPMC and Carbopol as release retarding polymers, Sodium bicarbonate and Citric acid as gas - generating agents and other excipients by direct compression process. Optimization studies have been done by Design Expert Stat Ease software using Central composite design. 13 formulations were prepared as suggested by the software. The pharmaceutical properties of formulations, their buoyancy lag time and total floating time and *in vitro* drug release were evaluated. The *in vitro* drug release studies indicated that the optimized formulation containing equal concentration of HPMC and Carbopol (F3) showed highest drug release of 99.87% and floating lag time of 68 seconds. The *in vitro* drug release data was treated with mathematical equations, and it was concluded that Amoxicillin trihydrate released from the tablet followed First order kinetics with non-fickian super case-II transport. In this study the effect of two release retarding polymers ie, carbopol and HPMC were also studied so as to improve the drug release, total floating time and hence improve its site specific action. From this study it was concluded that gastro retentive floating tablets of Amoxicillin trihydrate is a promising approach as it can decrease in the frequency of administration and ultimately provide better patient compliance by gastric retention.

KEYWORDS: Gastroretentive floating tablets, Amoxicillin trihydrate, Helicobacter pylori, Carbopol, HPMC, optimization.

1. INTRODUCTION

The oral route is the most predominant and preferable route of drug delivery due to the ease of administration by the patient, and therefore a highly convenient way for substances to be introduced into the human body. Oral drug delivery systems have progressed from conventional immediate release to site-specific delivery over a period of time. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastro intestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine. Hence, a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site.[1]

Gastro retentive floating tablet is an approach to prolong gastric residence time and also to provide site-specific drug release in the upper gastrointestinal tract for local or systemic effect. This controls the fluctuation in plasma drug concentration, improves bioavailability, therapeutic efficacy and also allow a possible reduction in the dose because of steady therapeutic levels of a drug. This system can be retained in the stomach and assists in improving the oral sustained delivery of the drugs that have an absorption window in a particular region of the GIT.[2]

Amoxicillin Trihydrate is a trihydrate form of Amoxicillin; a broad spectrum semisynthetic beta lactam antibiotic, which is effective for Helicobacter pylori mediated gastritis and peptic ulcer. H.pylori exists in the gastric mucous layer or epithelial cell surfaces. Thus, the concentration and resident time of Amoxicillin

Trihydrate in stomach would be effective for complete eradication of H.pylori. Due to short half life (1-1.5 hrs), low bioavailability (60%) and limited plasma protein binding (20%) of Amoxicillin trihydrate, multiple doses are needed to maintain constant plasma concentration for good therapeutic response. So, gastro-retentive drug delivery system is desirable to prolong the residence time of dosage form in the stomach until the drug is completely released from the system. Amoxicillin Trihydrate is considered as a good candidate for gastro-retentive floating tablets due to its high solubility in the stomach pH compared to its solubility in the small intestine pH.[3,14,15]

The present study was focused on the development of Amoxicillin trihydrate gastroretentive floating tablets by direct compression method using two release retarding polymers ie, Carbopol and HPMC and evaluation for the physical characters such as drug release, floating properties, swelling index and *in vitro* drug release study. Physical stability of developed optimized formulation for 3 months were also conducted. In this study the effect of two release retarding polymers ie, carbopol and HPMC were compared so as to improve the drug release, floating properties and hence improves its site specific action.

2. MATERIAL AND METHODS

Materials

2.1. Chemicals used

Amoxicillin trihydrate (Yarrow Chem Products, Mumbai), Carbopol (Loba Chemie, Mumbai), HPMC (Loba Chemie, Mumbai), Micro Crystalline Cellulose (Sisco research laboratories, Maharashtra), Magnesium stearate (Thomas baker, Mumbai), Citric acid (Isochem laboratories, Kochi), Sodium bicarbonate (Nice chemicals, Kochi), Talc (Sd fine- Chem Ltd, Mumbai), Hydrochloric acid (Finar, Ahmedabad).

2.2. Instruments used

Double beam UV Spectrophotometer (Systronics, UV-VIS Spectrophotometer117, Ahmedabad), FT-IR (Jasco model FT/IR 4100),10 station rotary tablet punching machine (Multispan, Ahmedabad), Dissolution apparatus (Electrolab, Mumbai), Electronic weighing balance (Prince scale industries, Ahmedabad), Friabilator (Roche friabilator), Pfizer hardness tester (Rolex, Haryana), Bulk density apparatus (Labtech, Mumbai).

Methods

❖ **Preformulation Study**

Preformulation studies is the type of study that focus on the various physicochemical properties of drug sample that may affect the performance of drug and development of dosage form. It is the first step in dosage development process. The main purpose of preformulation studies is to develop the stable, effective and safe dosage form by establishing kinetic rate profile and compatibility with other excipients.[4]

2.3. Analytical Methods

2.3.1. Determination of UV λ max

Dissolve accurately weighed 100 mg of Amoxicillin trihydrate in 100 ml of 0.1N HCl of pH 1.2 in 100ml standard flask to get 1mg/ml from the stock solution of Amoxicillin trihydrate, 1ml is pipetted out and diluted to 100ml with methanol to get 10µg/ml. The absorption maximum of standard solution of Amoxicillin trihydrate is determined by scanning the resulting stock solution in UV spectrometer at 200 - 600 nm. The absorption maxima obtained is compared with reference standard for the value.[5]

2.3.2. Preparation of Standard Calibration Curve of Amoxicillin trihydrate

A spectrophotometric method based on the measurement of absorbance at 270 nm in 0.1 N HCl was used in present study for the estimation of Amoxicillin trihydrate. The stock solution was freshly prepared by dissolving 100mg of Amoxicillin trihydrate in 10ml of methanol in a 100 ml volumetric flask and then making up the solution upto the mark using 0.1N HCl for obtaining the solution of strength 1000 µg/ml(stock I).This is considered as standard solution. From this stock 0.1, 0.5, 1, 1.5, 2.0, 3.0 and 3.5 ml were taken separately and made up to 10 ml with distilled water, to produce 10, 50, 100, 150, 200, 300 and 350µg/mL respectively. The absorbance was measured at 270nm using a UV-Visible spectrophotometer against 0.1 N HCl as blank and a calibration curve was plotted by taking concentration on x-axis and absorbance on y-axis.[5]

2.4. Physicochemical properties of drug

2.4.1. Identification of drug by IR Spectroscopy

For the identification of given drug the IR spectra of drug samples (Amoxicillin trihydrate) was compared with the standard IR spectra of pure drug.

2.4.2. Organoleptic properties

Drug was tested for colour, odour and taste and compared with official monograph.

2.4.3. Solubility of drug

Solubility test was conducted to determine its solubility in the dissolution medium and other solvents. Solubility of Amoxicillin trihydrate was observed in different solvents such as distilled water, 95% ethanol, 0.1N HCl (pH 1.2), methanol, chloroform, ether and fixed oils.

2.4.3. Drug –excipient compatibility

FTIR spectroscopic method was used for carried out drug-excipient compatibility study.FT-IR spectra of pure drug, Carbopol, HPMC and their physical mixtures were taken by KBr pellet technique between 400–4000cm^{-1}. Once spectra was recorded, the peaks of pure drug, polymers and physical mixtures of polymers and drug were compared for incompatibility.

2.5. Precompression parameters of powder blends

2.5.1. Bulk density and Tapped density[6]

10gm of powder was weighed. Weighed amount of given powder was introduced into measuring cylinder attached with bulk density apparatus. After that the initial volume was observed for bulk density and then cylinder was tapped continuously until no further change in volume was observed. Record the final volume for tapped density. Then bulk and tapped density were calculated by using the given formula.

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Initial volume}}$$

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

2.5.2. Carr's index

Carr's index is also known as compressibility index. It is significant number that can be obtained from bulk and tapped density. The compressibility of raw material and blend was determined by Carr's compressibility index by using given formula.

$$\text{Carr's index (\%)} = \frac{\text{(tapped density) - (bulk density)}}{\text{(tapped density)}} \times 100$$

2.5.3. Hausner's ratio

The Hausner's ratio is a number that indicates flowability of a powder. Hausner's ratio is calculated by given equation

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.5.4. Angle of repose

Maximum angle possible between the surface of a pile of powder and the horizontal plane are referred as angle of repose. Angle of repose used to measured frictional force leads to improper flow. Fixed funnel method was used for determining the angle of repose. The average value was taken and angle of repose was calculated by using the given equation.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where θ = Angle of repose, h = height of the heap, r = radius of the heap.

2.6. Compression of Tablet[7]

Technology Applied: Direct compression.

The key ingredients included in the formulations are.

- Release retarding Polymers: HPMC and Carbopol
- Effervescent agent: Sodium bicarbonate and Citric acid
- Diluent : Micro Crystalline Cellulose
- Glidant: Talc
- Lubricant: Magnesium Stearate.

Accurately weighed quantities of polymer and Micro crystalline cellulose were taken in a mortar and mixed geometrically, to this required quantity of Amoxicillin trihydrate was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate and Citric acid were taken separately in a mortar and powdered with pestle. The powder is passed through sieve no 40 and mixed with the Amoxicillin trihydrate blend which was also passed through sieve no 40. The whole mixture was mixed for 3 minutes. To this Magnesium stearate and Talc were added and mixed for 2 minutes. The mixture equivalent to 600 mg was compressed into tablets with rotary tablet punching machine.

Design Expert Stat Ease Software was used to design formulations. Thirteen formulations with variable concentrations of release retarding polymers *ie*, Carbopol and HPMC were suggested by the software. The formulation design is shown in table 1.

Table 1: Formulation design of floating tablets of Amoxicillin trihydrate.

Ingredients	F1 mg	F2 mg	F3 mg	F4 mg	F5 mg	F6 mg	F7 mg	F8 mg	F9 mg	F10 mg	F11 mg	F12 mg	F13 mg
Amoxicillin trihydrate	200	200	200	200	200	200	200	200	200	200	200	200	200
Carbopol 940P	150	----	150	----	150	75	75	75	75	75	75	75	----
HPMC	----	150	150	75	75	----	150	75	75	75	75	75	----
$NaHCO_3$	70	70	70	70	70	70	70	70	70	70	70	70	70
Citric acid	10	10	10	10	10	10	10	10	10	10	10	10	10
MCC	165	165	15	240	90	240	90	165	165	165	165	165	315
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	600	600	600	600	600	600	600	600	600	600	600	600	600

2.7. Post Compression Parameter (Evaluation)[17]

The prepared floating tablets were evaluated for general appearance, thickness, hardness, friability, weight variation, *In vitro* buoyancy, swelling index study, *In vitro* dissolution studies, and short term stability study.

2.7.1. General appearance

Organoleptic properties (General appearance) of tablet is the first most important quality for the acceptance of tablet. Its play a major role for the consumer acceptance. Prepared tablets was evaluated for organoleptic properties (colour, odour, taste and shape).

2.7.2. Thickness

13 tablets from each formulation were randomly selected and thickness was measured by using micrometer and then average value was calculated.[8]

2.7.3. Hardness

Hardness of tablet refer to the ability of a tablet to withstand for mechanical shocks. Hardness testing is used to test the breaking point of tablet.6 tablets were taken from each formulation. Hardness of tablet was determined by using Pfizer hardness tester. Hardness was expressed in Kg/cm^2.

2.7.4 Friability

Roche friabilator was used for the determination of friability and it is expressed in percentage. 20 tablets were taken, initially weighed (W initial). Preweighed selected tablets were placed in the friabilator which revolves at 25 rpm (100 revolutions) for 4 min. Then tablets were removed from the chamber de-dusted and weighed again (W final). The % friability was then calculated by the equation,

F= {(W initial) - (W final)/ (W initial)}×100

2.7.5. Weight variation

20 tablets were taken from each formulation randomly and weighed individually. Average weight was calculated and percentage deviation from the average weight was determined by using given formula.[9]

% deviation ={(Average weight – initial weight) /Average weight} X 100

Table 2: Percentage deviation in weight variation.

Sl. No	Average Weight	Maximum percentage difference allowed
1	130 or less	10
2	130-324	7. 5
3	More than 324	5

2.7.6. Drug content determination

Twenty tablets were taken, powdered and the powder equivalent to one dose each was transferred to a 100 mL volumetric flask and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and diluted suitably and Amoxicillin trihydrate content in the samples was estimated using UV- Visible spectrophotometer at 270 nm. Drug content was determined from standard calibration curve of Amoxicillin trihydrate.[10]

2.7.7. *In vitro* buoyancy/ floating study

In-vitro buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing 0.1N HCL pH 1.2. The time taken for the tablet to rise to the surface and float was floating lag time and the duration of time the dosage form constantly remained on the surface of medium was determined as total floating time (TFT).[10]

2.7.8. Swelling index

The swelling of the polymers can be measured by their ability to absorb water and swell enormously. The swelling index is the ability of the polymers to swell by absorbing water. The water uptake study of the tablets was carried out by using 500 ml of beaker. The tablets were placed in 0.1N HCl containing beaker. The tablets were withdrawn from the medium at different time interval, excess water removed by blotting and weighed.[9]

The swelling index of the tablets was given by following formula.

$$\textbf{Swelling index(\%)} = \frac{\text{weight of swollen tablet} - \text{initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

2.7.9 *In vitro* dissolution studies

In vitro dissolution studies of floating tablets were carried out by using USP type II apparatus (paddle type). Dissolution vessel was filled with 900ml 0.1 N HCL pH 1.2 and then temperature of the medium was adjusted to 37 ± 0.5^0C. Rotational speed of paddle was set at 50 rpm and then one tablet was introduced in each dissolution vessel.10ml solution were withdrawn from the dissolution vessels at every hour for 8 hrs and the samples were replaced with 10ml fresh dissolution medium. Absorbance of this solution was measured at 270 nm using a UV spectrophotometer.

2.7.10. Optimization by Design Expert Stat Ease Software

Statistical design of experiments, a computer-aided optimization technique, was used to identify critical factors, their interactions and ideal process conditions that accomplish the targeted response. The best formulation was determined using Design Expert Stat Ease Software. Central composite design was used for the optimization. In this study, carbopol and HPMC were selected as the two factors and floating lag time and *in vitro* drug release were considered as the two responses. Hence, thirteen experimental trials were done. Countour plots were drawn and optimum formulation was selected by optimization criteria. The floating tablet with low floating lag time and high *in vitro* drug release was fixed as QTPP(Quality Target Product Profile), floating lag time and *in vitro* drug release data were set as the CQA (Critical Quality Attribute) and carbopol and HPMC were selected as the CMA (Critical Material Attribute).[10,11,12,13]

2.7.11. Drug release kinetics

In order to understand the exact mechanism of drug release from the dosage form, the data of *in vitro* dissolution study of optimized formulation F3 was fitted in to various kinetics equations (zero order, first order, Higuchi model and Korsmeyer Peppa's model).

2.7.12. Short term stability study

From the prepared Amoxicillin trihydrate floating tablets, optimized formulation (F3) with highest *in vitro* drug release pattern and lowest floating lag time were packed in high density polyethylene bottle and subjected to stability studies. This study was carried out at temperature and humidity conditions as per ICH guidelines and the tests were carried out in a stability chamber. The temperature and humidity conditions used were, 40ºC ± 2ºC at 75% ± 5% RH, 25ºC ± 2ºC at 60% ± 5% RH, 5ºC ± 3ºC.Samples were withdrawn at 0 day, 30 days and 90 days time intervals and evaluated for hardness, friability, drug content, floating lag time and *in vitro* drug release.[16]

3. RESULTS AND DISCUSSION

3.1. Analytical method

3.1.1. Determination of UV λ max

The pure drug of Amoxicillin trihydrate was scanned by UV spectroscopy and λmax was found to be 270 nm.

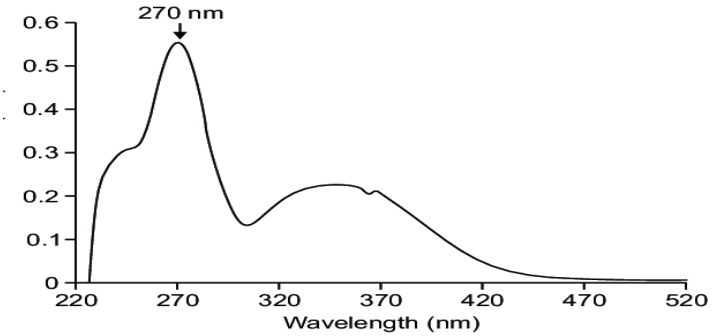
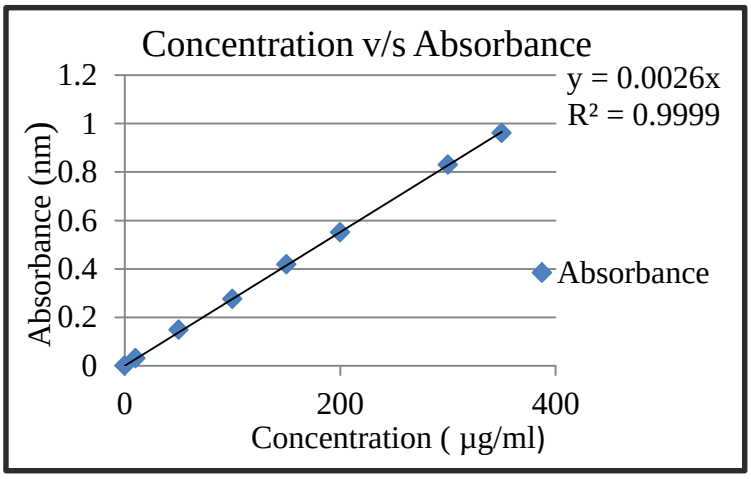


Fig. 1: UV spectrum of Amoxicillin trihydrate in 0.1N HCl of pH 1.2.

3.1.2. Calibration curve of Amoxicillin trihydrate

Table 3: Absorbance values for Amoxicillin trihydrate.

Concentration (µg/ml)	Absorbance (at 270nm) ± SD
0	0 ± 0.02
10	0.031 ± 0.01
50	0.149 ±0.04
100	0.276 ±0.02
150	0.419 ±0.03
200	0.551 ±0.01
300	0.830 ±0.06
350	0.962 ±0.03



All values are expressed as mean ± SD, n = 3

Fig. 2: Standard calibration curve of Amoxicillin.

trihydrate in 0.1N HCl of pH 1.2 at 270nm

The drug was scanned in UV region (200-600 nm) by preparing 1mg/ml solution using 0.1N HCl of pH 1.2 to find out wavelength of maximum absorption (λ max). The λmax was found to be 270 nm. So the standard calibration curve of Amoxicillin trihydrate was developed at this wavelength. Standard calibration curve of Amoxicillin trihydrate was determined in 0.1N HCl of pH 1.2 by plotting absorbance against concentration at 270 nm. The calculation of drug content, *in vitro* drug release and stability studies are based on this calibration curve.

3.2. Physico-chemical properties of drug

3.2.1. Organoleptic properties

Organoleptic properties of Amoxicillin trihydrate was studied and it was concluded that, Amoxicillin trihydrate is a white crystalline powder, odourless and slightly bitter in taste.

3.2.2. Solubility profile

Solubility studies were carried out in different solvents and it was found that AMT was highly soluble in 0.1N HCl, slightly soluble in distilled water, ethanol and methanol and insoluble in chloroform, ether and fixed oils. The results complies with the pharmacopoeia specifications. Amoxicillin trihydrate shows a pH dependent solubility. It is highly soluble in acidic pH than alkaline pH.

3.2.3. Identification and Compatibility by FTIR studies

FTIR studies were conducted in pure Amoxicillin trihydrate and physical mixture of drug with carbopol and HPMC. The FTIR spectrum is shown below.

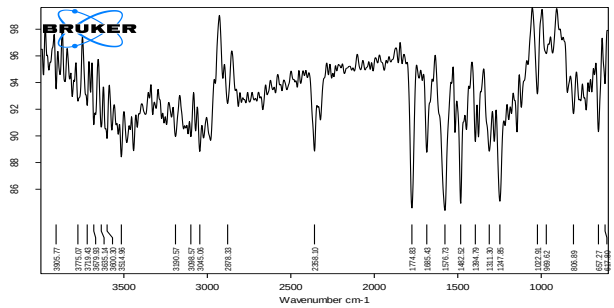


Fig. 3: FTIR spectrum of Amoxicillin trihydrate

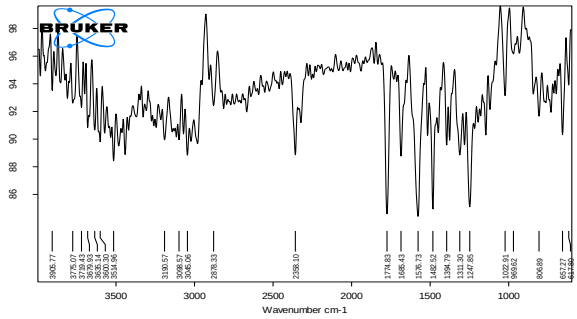


Fig. 4: FTIR spectrum of physical mixture (Amoxicillin trihydrate + Carbopol).

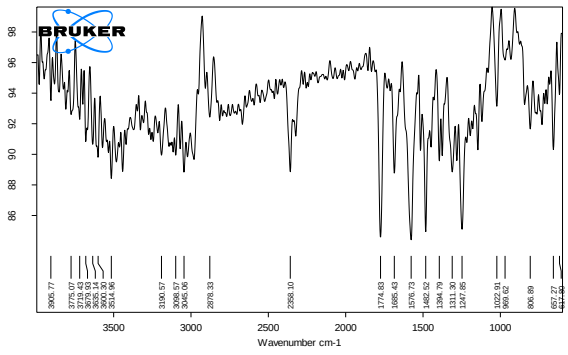


Fig.5: FTIR spectrum of physical mixture (Amoxicillin trihydrate+HPMC)

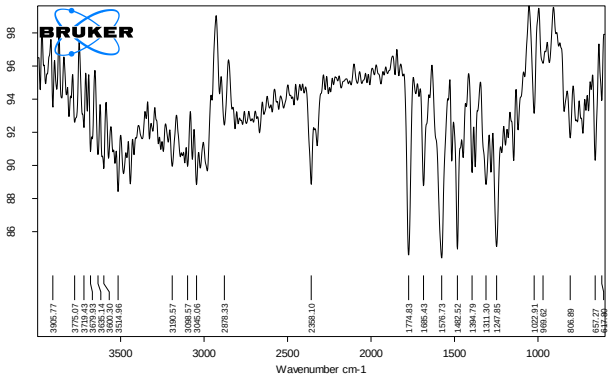


Fig.6: FTIR spectrum of physical mixture (Amoxicillin trihydrate+HPMC+Carbopol)

Drug identification is done by performing FT-IR studies. During FT-IR studies, the peaks of Amoxicillin trihydrate was obtained at 3514.96 cm^{-1} (O-H Stretching), 3045.06 cm-^{1}(C-H Stretching due to benzene ring),2878.33 cm^{-1}(C-H Stretching due to methyl group),1774.83 cm^{-1} (C=O Stretching due to Beta lactum ring), 1685.43cm^{-1}(C=O Stretching due to Amide group) etc. There is no significant change in the peak of the pure drug in the FTIR spectrum of physical mixture of pure drug with the release retarding polymers, ie., carbopol and HPMC. It indicates that there is no chemical interaction between the drug and the polymers. This shows that Amoxicillin trihydrate was compatible with both the polymers.

3.3. Precompression parameters of powder blend

Table 4: Precompression parameters of powder blend.

Formulation	Bulk density ±SD (g/ml)	Tapped density ± SD (g/ml)	Carr's index ± SD (%)	Hausner's ratio ± SD	Angle of repose ± SD (θ)
F1	0.525 ± 0.62	0.640 ± 0.62	13.66 ± 0.62	1.143	25.98˚± 0.11
F2	0.536 ± 0.62	0.644 ± 0.62	13.64 ± 0.62	1.162	26.41˚± 0.09
F3	0.546 ± 0.62	0.668 ± 0.62	13.99 ± 0.62	1.187	27.16˚± 0.09
F4	0.53 ± 0.62	0.648 ± 0.62	13.72 ± 0.62	1.158	28.15˚± 0.14
F5	0.529± 0.62	0.663 ± 0.62	13.76 ± 0.62	1.183	27.34˚± 0.21
F6	0.531± 0.62	0.652 ± 0.62	13.62 ± 0.62	1.17	27.2˚± 0.11
F7	0.543 ± 0.62	0.668 ± 0.62	13.98 ± 0.62	1.186	26.78˚± 0.22
F8	0.538 ± 0.62	0.642 ± 0.62	13.86 ± 0.62	1.15	27.25˚± 0.13
F9	0.538 ± 0.62	0.642 ± 0.62	13.86 ± 0.62	1.15	27.25˚± 0.13
F10	0.538 ± 0.62	0.642 ± 0.62	13.86 ± 0.62	1.15	27.25˚± 0.13
F11	0.538± 0.62	0.642 ± 0.62	13.86 ± 0.62	1.15	27.25˚± 0.13
F12	0.538 ± 0.62	0.642 ± 0.62	13.86 ± 0.62	1.15	27.25˚± 0.13
F13	0.532 ± 0.62	0.643 ± 0.62	13.66 ± 0.62	1.16	28.35˚± 0.26

All values are expressed as mean ± SD, n = 3

3.3.1. Bulk density and Tapped density

The bulk density and tapped density of the powder blend was in the range of 0.525 to 0.546 g/ml, 0.640 to 0.668 g/ml respectively and which indicates that the powder blend were not bulky and has good packaging characteristics. The results were shown graphically.

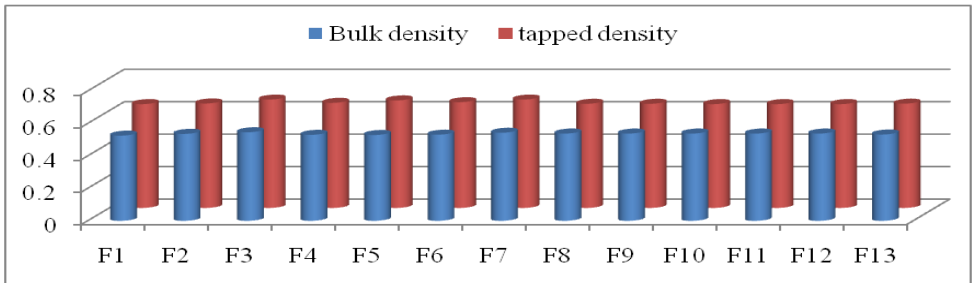


Fig.7: graphical representation of bulk density and tapped density in different batches of formulation.

3.3.2. Compressibility Index (CI)

Compressibility index were found in between 13.62 to 14.25%, which indicates that the powder blend have excellent flow property for compression.

3.3.3. Hausner's ratio

The hausner's ratio of the powder blend was found to be in the range of 1.143 to 1.187, which indicates good flow properties of powder blend.

3.3.4. Angle of repose (θ)

The angle of repose for the formulated powder blends were found to be in the range of 25.98˚ to 28.38˚, which indicates excellent flow properties of powder blend.

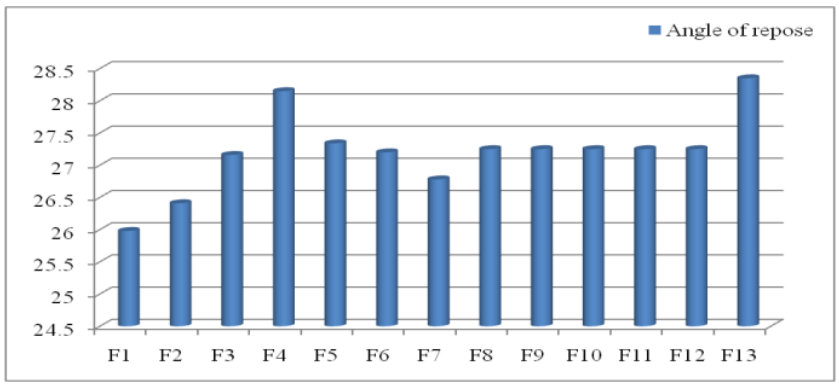


Fig.8: Graphical representation of Angle of repose in different batches of formulation.

3.4. Post compression parameters of floating tablets.

Table.5: Post compression parameters of floating tablets.

Formulation	Average thickness ± SD (mm)	Hardness ± SD(Kg/cm^2)	Percentage friability(%)	Weight variation (%)	% Drug Content ±SD (%)
F1	3.53 ± 0.62	5.3 ± 0.39	0.32%	1.38 ±0.43	95.52 ± 0.15
F2	3.58 ± 0.62	5.32 ± 0.62	0.33%	1.46 ±0.40	96.3 ± 0.23
F3	3.7 ± 0.62	5.6 ± 0.62	0.25%	1.28 ±0.71	98.49 ± 0.12
F4	3.48 ± 0.62	5.2 ± 0.48	0.36%	1.43 ±0.41	98.16 ± 0.22
F5	3.67 ± 0.62	5.4 ± 0.62	0.29%	1.32 ±0.74	97.24 ±0.34
F6	3.46 ± 0.62	5.2 ± 0.37	0.33%	1.39 ±0.49	98.04 ± 0.4
F7	3.68 ± 0.62	5.5 ± 0.62	0.28%	1.3 ± 0.33	98.28 ± 0.23
F8	3.57 ± 0.62	5.35 ± 0.62	0.33%	1.55± 0.49	95.38 ± 0.15
F9	3.56 ± 0.62	5.34 ± 0.62	0.35%	1.55 ±0.49	95.52 ± 0.23
F10	3.62 ± 0.62	5.39 ± 0.62	0.36%	1.55 ±0.49	95.37 ± 0.12
F11	3.58 ± 0.62	5.36 ± 0.62	0.36%	1.55 ±0.49	95.78 ± 0.22
F12	3.59 ± 0.62	5.38 ± 0.62	0.35%	1.55 ±0.49	95.46 ± 0.34
F13	3.38 ± 0.62	5.06 ± 0.62	0.4%	1.74 ±0.56	95.35 ± 0.76

All values are expressed as mean ± SD, n = 3

3.4.1 General appearance

The formulated tablets were white, flat, and round shaped without any scoring on any sides. All the tablets were elegant in appearance.

3.4.2. Thickness and Hardness

The measured thickness of each formulations was ranged between 3.38 to 3.7 mm which were found to be uniform. The measured hardness of tablets of each batch ranged between 4.2 to 6.2 kg/cm^2. This ensures good handling characteristics of all batches.

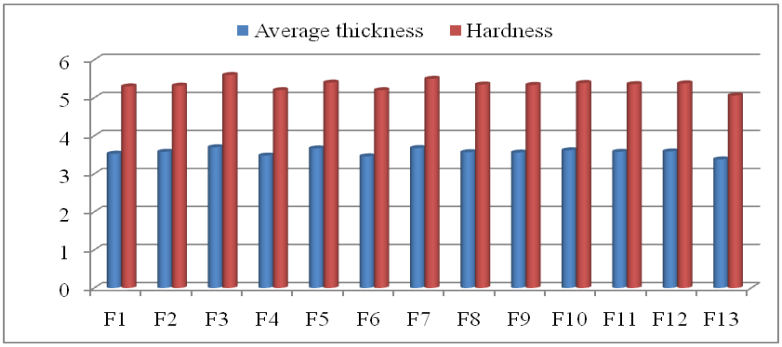


Fig.9: graphical representation of average thickness and hardness in different batches of formulations.

3.4.3. Friability test.

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

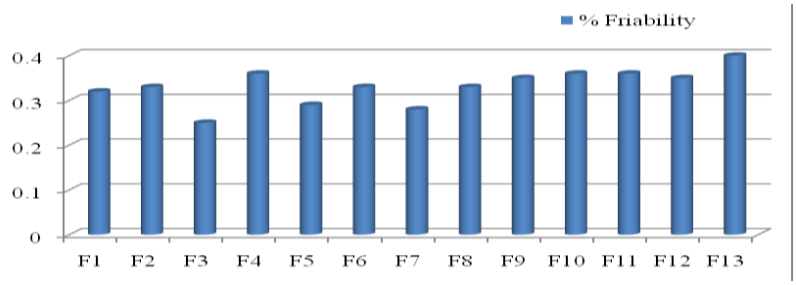


Fig.10: graphical representation of % friability in different batches of formulation.

3.4.4. Weight variation test

All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of 5 % of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

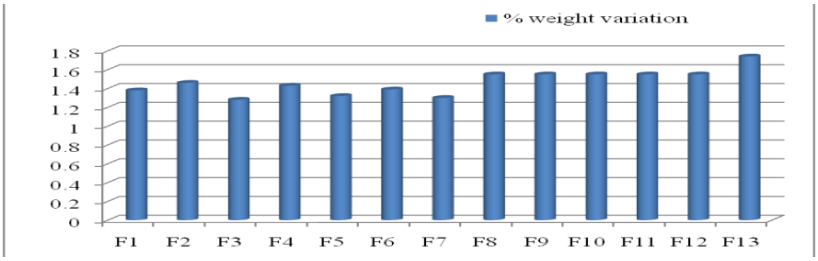


Fig.11: graphical representation of % weight variation in different batches of formulation.

3.4.5. Percentage drug content

Drug content of formulated floating tablets were estimated by UV spectrophotometer at λmax 270 nm and the drug content was calculated from the calibration curve. Among all the 13 formulations, F3 showed greater drug content, *ie.*, 98.49 %.

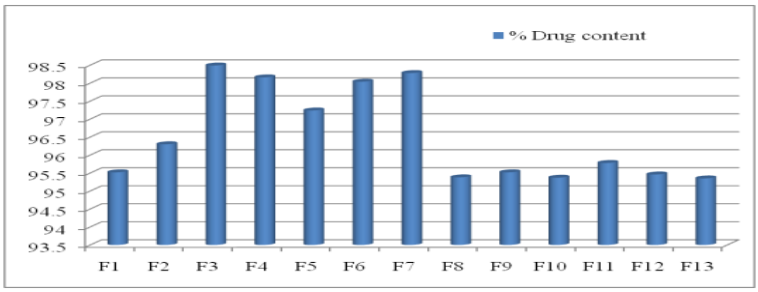


Fig.12: graphical representation of % drug content in different batches of formulation.

3.4.6. *In vitro* buoyancy study

Table.6: floating lag time and total floating time of all formulations.

Formulation	Floating lag time (Sec)	Total floating time (hr)
F1	128	< 12
F2	45	< 8
F3	68	>12
F4	56	< 8
F5	97	> 12
F6	92	> 12
F7	70	> 12
F8	85	> 12
F9	86	> 12
F10	84	> 12
F11	85	> 12
F12	86	> 12
F13	58	< 0.5

On immersion in 0.1N HCl solution of pH (1.2), the tablets floated, and remained buoyant without disintegration. Table 6 shows the results of Buoyancy study. From the results it can be concluded that the batch containing only HPMC polymer showed lowest Buoyancy lag time (BLT) and Total floating time (TFT) (< 8 hrs) because it partially disintegrated within 8hrs.Formulation containing carbopol showed highest BLT of 128 sec, while the formulation containing carbopol (alone) did not float more than 10 hrs. This may be due to high moisture gain and swelling of tablet, which decreases its floating ability leading to variation in BLT and TFT. The formulations containing combination of polymers showed good floating characters.

At 0 min **After 68 sec** **After 1 hr** **After 12 hr**

Fig.13: *in vitro* floating behavior of formulation F3.

3.4.7. Swelling index study

Fig.no.14: % swelling index of all formulations.

Before swelling **After swelling**

Fig.no.15: swelling behavior of F3.

Swelling study was performed on all the batches for 12 hrs. From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form. In the present study, the higher swelling index was found for tablets of batch F1 containing carbopol.

3.4.8. In vitro drug release studies

The *in vitro* drug release of all the 13 formulations were determined using USP II Paddle apparatus with 0.1N HCl as dissolution medium. Among all the formulations, F3 showed greater prolonged *in vitro* drug release (99.87%) than all other formulations for more than 12 hrs. The F13 formulation which is prepared without any polymers shows almost complete drug release within 3hrs. So, this formulation can't show prolonged drug release. The formulations prepared with combination of carbopol and HPMC shows best *in vitro* drug release characteristics than the formulation with a single polymer.

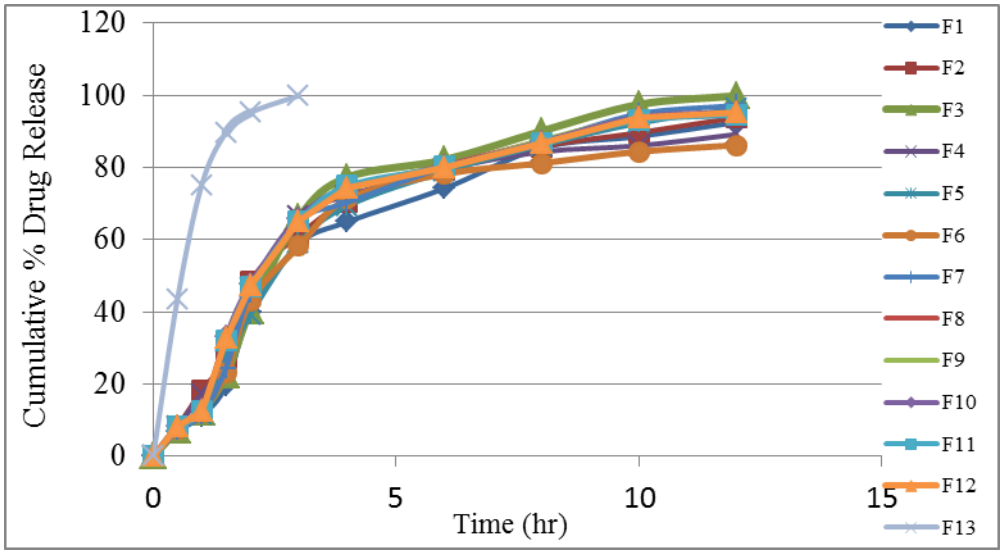


Fig. 16: *In vitro* drug release of formulations

3.5. Optimization by Design Expert Software.

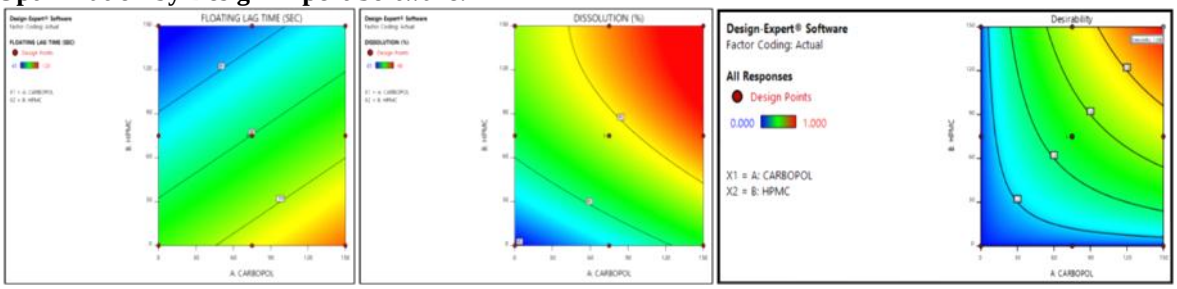


Fig. 17: Countour plot showing the effect of carbopol and HPMC on.
(a) Floating lag time (b) *in vitro* drug release (c) desirability.

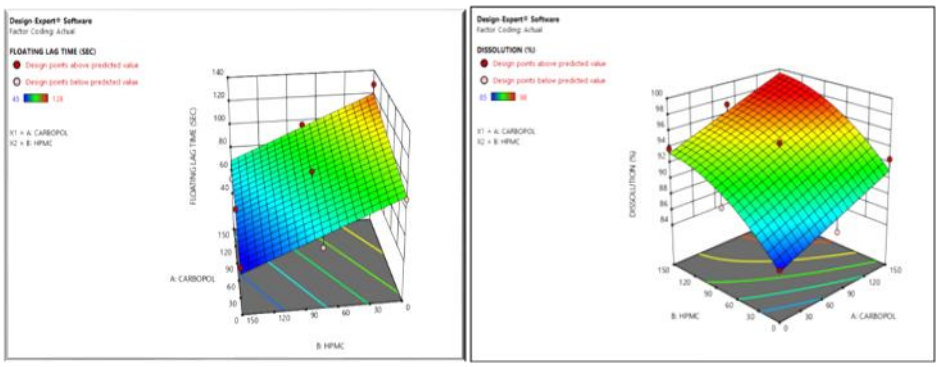


Fig.18 : 3-D surface response plot showing the effect of carbopol and HPMC on
(a) Floating lag time (b) *in vitro* drug release.

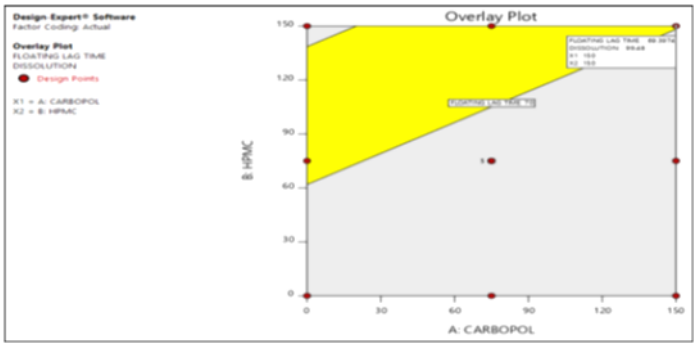


Fig. 19 : Overlay plot.

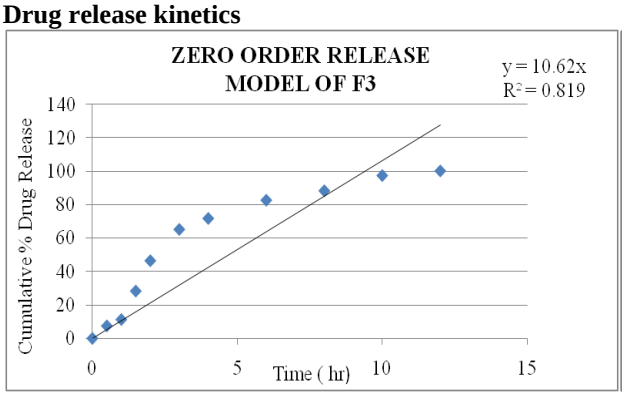
Optimization was done by Design Expert Stat Ease Software version 13.0.7.0. Two factors were selected for optimizing the formulation. The factors selected were Carbopol and HPMC. Central composite design was used for optimization. To determine the best formulation, 2 responses ie., floating lag time and *in vitro* drug release were considered.13 formulations were suggested by the software. After the analysis of the optimized data, 3 solutions were obtained and one was selected by considering the floating lag time and *in vitro* drug release of the formulation.

The batch with Carbopol-150 mg and HPMC-150 mg with desirability 1 was found to be optimum. From this data, formulation F3 was selected as the optimized formulation having highest *in vitro* drug release (99.87%) and lowest floating lag time (68 sec). Hence F3 was selected as optimized formulation.

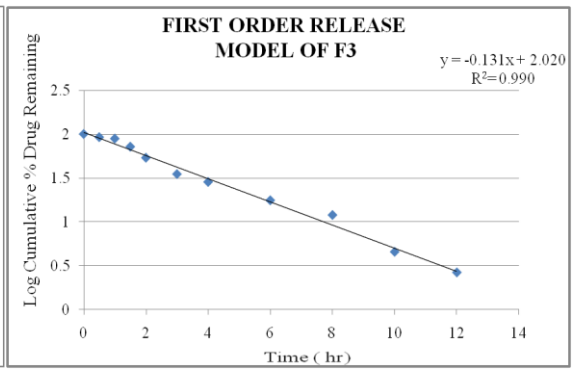
Fig.20: Photograph of optimized formulation – F3.

Out of 13 formulations prepared, the formulation F3 was the optimized formulation. The data obtained from drug release profile was fitted into various models to determine the drug release kinetics and mechanism.

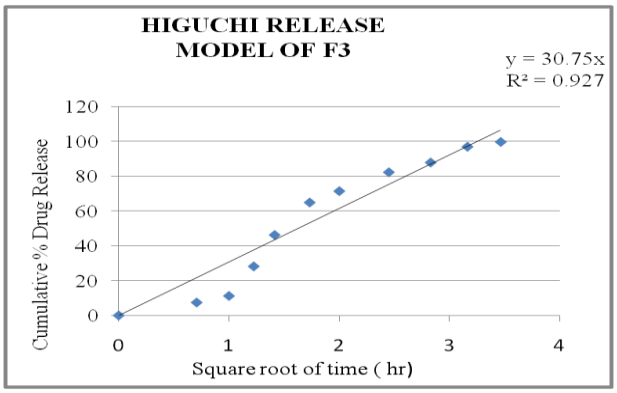
3.6. Drug release kinetics



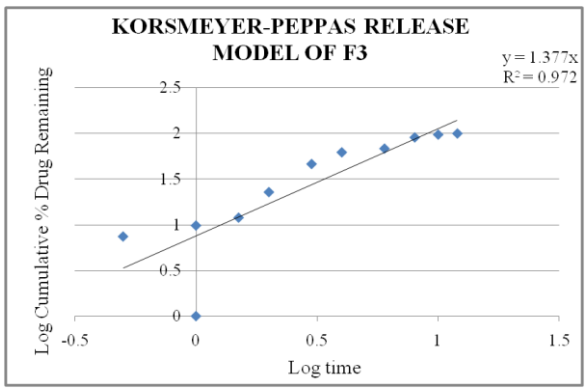
(a)



(b)



(c)



(d)

Fig. 21: (a) Zero order release plot (b) First order release plot. (c) Higuchi release plot (d) Korsmeyer-peppas plot.

Table.7: Drug release kinetics of optimized formulation – F3.

Formulation code	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	n
F3	0.819	0.990	0.9273	0.972	1.377

In F3, correlation coefficient of zero order kinetics was found to be 0.819, first order release kinetics was 0.990 and Higuchi plot was found to be 0.9273. Hence the formulation follows first order kinetics. To confirm the exact mechanism of drug release from the floating tablets, data was fitted according to Korsmeyer-Peppa's plot. The value of slope of plot n gives indication of release mechanism when n=1, release is independent of time ie zero order. If n= 0.5, then release is fickian diffusion. If n=0.5 -1, diffusion is non-fickian and n>1 then it is super case transport. The 'n' exponent value of best batch was 1.377. Hence it shows non-fickian super-case II transport mechanism.

3.7. Stability studies

Table 8: Stability data of optimized formulation – F3.

STORAGE CONDITION	SAMPLING INTERVAL	HARDNESS (Kg/cm^2)	FRIABILITY (%)	DRUG CONTENT (%)	FLOATING LAG TIME (Sec)	*IN VITRO* DRUG RELEASE (%)
40ºC ± 2ºC at 75% ± 5%RH	Initial study	5.6 ± 0.62	0.25	98.49 ± 0.12	63	99.87
	30 days	5.6 ± 0.57	0.252	98.15 ± 0.99	65	98.92
	90 days	5.6 ± 0.39	0.256	97.56 ± 0.24	66	97.77
25ºC ± 2ºC at 60% ± 5% RH	Initial study	5.6 ± 0.62	0.25	98.49 ± 0.12	63	99.87
	30 days	5.6 ± 0.60	0.252	98.32 ± 0.23	64	99.05
	90 days	5.6 ± 0.45	0.254	98.08 ± 0.58	65	98.96
5ºC ± 3ºC	Initial study	5.6 ± 0.62	0.25	98.49 ± 0.12	63	99.87
	30 days	5.6 ± 0.53	0.255	98.12 ± 0.56	65	98.95
	90 days	5.6 ± 0.42	0.258	97.59 ± 0.78	66	98.04

All values are expressed as a mean ± SD, n = 3

From the prepared 13 formulations, the optimized formulation F3 was used for stability studies as per ICH Guidelines for 3 months. It showed that the prepared floating tablets passed stability studies with not much significant changes in hardness, friability, drug content, floating lag time and *in vitro* drug release.

4. CONCLUSION

Amoxicillin trihydrate gastro retentive floating tablets were successfully developed using carbopol and HPMC as release retarding polymers and sodium bicarbonate and citric acid as gas generating agents by direct compression technique. The developed formulations were then characterized for their hardness, thickness, friability, weight variation, drug content, *in vitro* buoyancy, swelling index, *in vitro* drug release and stability studies. FT-IR studies for drug and excipients revealed that there is no incompatibility or interaction between drug and excipients.

The floating tablets (F3) prepared using Carbopol and HPMC as release retarding polymers in 1:1 ratio (carbopol-150 mg, HPMC- 150 mg) was found to show better result in floating properties and *in vitro* drug release. Also this formulation F3 shows resemblance with the optimized solution suggested by the Design Expert Stat Ease software and hence selected as optimized formulation. The kinetic studies was better explained by first order drug release and Korsmeyer-Peppas plot which indicated non-fickian super case II transport. The stability studies indicated that the formulation remained stable as no significant changes occurred. So the optimized formulation was found to be stable.

The results of present study suggested further investigations for F3 on evaluation of long term stability studies, and investigation on *in vivo* performance using animal models. The gastro retentive floating tablets of Amoxicillin trihydrate may be an advantageous formulation for oral sustained release and be helpful for the treatment of peptic ulcers. It can lead to decrease in the frequency of administration and better patient compliance.

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