EMPRO

Current Research in Pharmaceutical Sciences

Available online at www.crpsonline.com

ISSN: 2250 – 2688

Received: 29/11/2020
Revised: 20/12/2020
Accepted: 26/12/2020
Published: 31/12/2020

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DOI: 10.24092/CRPS.2020.100403

Website: www.crpsonline.com

Quick Response Code:

Formulation and Development of Bilayer Floating Tablet of Amoxicillin

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ABSTRACT

Bilayer floating tablet of amoxicillin was formulated successfully and evaluated under suitable parameters. All the batches of tablet produced were found to exhibit short floating lag times. The tablet of batch F2 exhibited a longer floating lag time of 23 minutes. Relationship between the dependent and independent variables was further elucidated using contour and response surface plots. Dissolution profiles that the tablets of batch F3, F7, and F12 exhibits initial burst phase during the first hour of dissolution. The burst phase was followed by a limited drug release for the rest of the period. Also it was observed during the dissolution studies that tablets of all three batches eroded quickly with increased effervescence. Time required for 50 % drug to get released ($T_{50\%}$) and $\%CR_{10hrs}$ were found to be in the range of 0.7 to 8.6 hours and 57.35 ± 3.89 to 99.93 ± 0.07 respectively, value of "Prob > F" less than 0. 05. Response surface plots and Contour plot indicated that at a fixed level of B (35 mg) and low level of A (amount of HPMC), % CR_{10hrs} increases from 68.11 to 90.00 % and $T_{50\%}$ decrease from 6.86 to 1.66 as the amount of citric acid (C) increases from 0 to 10 mg. Stability study was performed for optimized formulation and it was found that formulation was stable for 6 week at 25 °C/ 60% RH.

Key words: Bilayer floating tablet, amoxicillin, Evaluated, Multi-layered tablet, Stability

1. INTRODUCTION

Bilayer means a type of multi-layered tablet which have two layers instead of single layers. It was formed when two incompatible drugs were combined together in same formulation. In pharmaceutical companies, bilayer floating tablets are used to avoid chemical incompatibilities between the ingredients. It can enable the development of different drug release pro-files[1]. These tablets remain buoyant in the stomach. It cannot affect the gastric emptying rate and it may prolong the effect of tablet[2]. The combination of two or more API can helps in increases the patient convenience, pharmaceutical industries and compliance. As compared to conventional single layer tablets, Bilayer tablets has the most important advantages.[3] By physical separation, these tablets avoid the chemical incompatibility of formulation component. It enabled the controlled delivery of API with pre-determined release profile combining layer.[4] These tablets are most suitable for combination of two drugs. It I also used for sustained release tablets. In which one layer contained initial dose and second layer contains maintenance dose[5]. Different types of bilayer floating tablet are (1) Single sided tablet press, (2) Double sided tablet press, (3) Multilayer compression, (4) Bilayer tablet press with displacement monitoring[6].

Amoxicillin is a semi-synthetic derivative of penicillin. The structure is similar to ampicillin. It is a member of the penicillin family It shows better absorption when taken by oral administration. It has higher concentration in blood and in urine[7]. It can cross the placenta. It may be excreted into breast milk. It is metabolized in liver and may excreted through urine. the Formulation and statistical optimization of GRDFs containing amoxicillin, which would remain in stomach and/or upper part of GIT for prolonged period of time in view to maximize the bioavailability.

2. MATERIALS AND METHODS

Amoxicillin trihydrate of pharmaceutical grade and all grades of hydroxypropyl methyl cellulose (HPMC) were obtained as a gift sample, respectively. Analytical grades chemicals and reagents were used.

2.1 Pre Formulation Studies

2.1.1 Standard Curve of Amoxicillin Trihydrate

Addition of Amoxicillin (12 mg) was to phosphate buffer of pH 1.2 into a volumetric flask of 100mL for obtaining drug concentration of 20µg/ml. By using this solution, different type of concentrations is made 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20µg/ml. By the using of ultraviolet spectrophotometer these concentrations are absorb at 230 nm against 0.1 N HCl blank. These were done for 3days to evaluate intra and inter day variations.

2.1.2 Amoxicillin Solubility in Different Solvents

The solubility was carried out in different solvents like methanol, ethanol and water. A pinch of drug was added into separate test tubes, containing 5 ml of each solvent. All the test tubes were shaken for 5-10 min.

2.1.3 Determination of Melting Point

Capillary fusion method was used to determine the melting point of Amoxicillin using melting point apparatus. The melting point was recorded and compared with literature value.

2.1.4 Partition Coefficient Study

Equal volume of n-octanol and double distilled water were saturated for a period of 24 h. 10 mg of Amoxicillin was added to the mixture and was agitated for 1 h. Water phase was then diluted suitably and absorbance was taken at λ_{max} 230 (nm). Partition coefficient was calculated as the ratio of drug concentration in n-octanol to that in the water using equation:

$$\mathbf{P_{o/w} = (C_{Oil} / C_{water})\ equilibrium}$$

2.2. Amoxicillin Sustained Release Layer Preparation

HPMCK4M, HPMCK15M and Carbopol P-940 were used for formation of Sustained release layers of Amoxicillin with direct compression method. At first Amoxicillin was weighed and passed through sieve no. 40. Other compounds which were used with Amoxicillin are HPMC, Carbopol, sodium bicarbonate, citric acid, lactose was weighed and passed through sieve no. 60. Sustained release layer was prepared by direct compression method using single punch tablet compression machine.

2.3 Pre Compression Perimeter

2.3.1 Determination of Particle Size

For particle size determination Sieve method is very much helpful. Different sieves are (20, 25, 30, 35, 40, 70 and 100) were selected and stand on each one top. 150 g of powder was placed on the top of the sieve and shake it. After 15minutesof shaking the amount of particle on each sieve were collected. By the using of following equation the average diameter of powder was calculated:

$$d = \frac{\sum x_i d_i}{100}$$

where, x_i = upper and lower sieve average size, d_i = range of bulk.

2.3.2 Bulk Density

A weighed powder was introduced in to the measuring cylinder and then the volume was noted. Bulk density was expressed in g/ml and determined by the following formula:

$$\rho\ \text{bulk} = \frac{m}{V\,\text{bulk}}$$

2.3.3 Tapped Density

A weighed powder was introduced in to the measuring cylinder. The cylinder was hit every 2seond from the height of 2.5 cm up to volume plateau. Tapped density was calculated from the following formula:

$$\rho\ \text{tapped} = \frac{m}{V\,\text{tapped}}$$

2.3.4 Compressibility

compressibility index helps to explain the flow properties of the powders. It was expressed in percentage. It gives following equation:

$$\text{Compressibility index} = 100 \times \frac{\text{tapped density} - \text{bulk density}}{\text{Tapped density}}$$

2.3.5 Hausner's Ratio

Hausner ratio is used for the measurement of powder flow. It was calculated by the following formula: -

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

2.3.6 Angle of Repose

Fixed funnel method were used to measure the angle of repose. Drugs which contain different excipient were prepared and weighed it then transfer into a funnel. A funnel was just touch the apex of the heap of the drug. These powders now allow to flow on the surface freely. The height (H) and radius (R) were measured and angle of repose were calculated by the formula:

$$\text{Angle of repose } (\theta) = \tan^{-1}\left(\frac{h}{r}\right)$$

2.4. Evaluation of Floating Tablets

The prepared tablets were further evaluated for hardness, thickness, weight variation, friability, content uniformity, floating lag time, total floating time and drug release studies.

2.4.1 Hardness

Hardness of the tablets indicated the with stand mechanical shocks while handling. Monsanto hardness tester was used to check the hardness of the tablets. These machines allow to measure. the harness, thickness and diameters. Formulations of tablets were randomly picked and use to determine the hardness of the tablets. The hardness of Amoxicillin tablet layer is shown.

2.4.2 Weight Variation

Eighteen tablets were weighed and the average weight was calculated. These weights were then compared with the average weight. If the tablets are not fall outside the limit percentage and also the tablets differ from more than double percentage limit these types

2.4.3 Friability

Eighteen tablets were weighed and put into the friabilator and continue for 4mins at 25 RPM. After that the tablets were then weighed again. The two weights were used to calculate friability as follows:

$$\text{Friability test} = \frac{\text{Weight of tablets before test} - \text{weight after test}}{\text{weight of tablets after test}} / 100$$

2.4.4 pH of Solution

Randomly pick one tablet and dissolved in purified water. After dissolution of tablet, the pH of the solution was measured by a pH meter. For each formulation this test were repeated 3 times.

2.4.5 Carbon Dioxide Content

In 100 ml of sulfuric acid, one effervescent tablet was dissolved. Before and after dissolution 1 N and weight variation was measured. CO_2 content was presented as mg. For each formulation this test was repeated 3 times.

2.4.6 Effervescence Time

By the help of stopwatch effervescence time were measured. In this a tablet was placed in a glass containing purified water and measured the effervescence time.

2.4.7 Thickness

Thickness of tablets was measured by using a calibrated dial calliper. Tablets of each formulation were evaluated.

2.4.8 Assay

Randomly select a tablet and put it into a 100 ml volumetric flask and then dissolved it into a phosphate buffer pH 5. After completion of dilution, UV spectrophotometer was used to determine the amount of the drug at 230 nm against with blank. Tablets of each formulation were evaluated.

2.4.9 Water Content

Formulation of each tablet was weighed and put it into the Desiccator for 4hours. Desiccator contained activated silica gel. Percentage of Water contain were calculated by following equations: -

$$\text{Water content} = \frac{\text{weight before drying} - \text{weight after drying}}{\text{weight before drying}} / 100$$

2.4.10 Equilibrium Moisture Content

At 18°C temperature tablets were placed in desiccators. These contain saturated saline solutions, potassium nitrate relative humidity (90%), sodium chloride (71%) and sodium nitrite (60%). By the using of Karl-Fisher method the percent equilibrium moisture content was determined using Autotitrator instrument.

2.4.11 Floating Property Study

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the

dosage form constantly remain on surface of medium is called the total floating time (TFT).

One tablet from each batch was taken in USP XXIII type II dissolution apparatus containing 900 ml of 0.1 N HCl. The study was performed at the paddle rotational speed of 50 rpm and bath temperature of 37 ± 0.5 °C. The time taken for tablet to emerge on surface of medium and the duration of time the tablet constantly remain on surface of medium was recorded as the floating lag time and TFT respectively.

2.5 Treatment of Dissolution Data With Different Model

Costa et al. suggested that the dosage forms that do not disaggregate and release the drug slowly could be represented by zero order kinetic equation. Colombo et al. suggested that the quantity of drug released from matrix tablets is often analysed as a function of the square root of time, which is typical for systems where drug release is governed by pure diffusion. However, the use of this relationship in swellable system is not justified completely as such systems can be erodible. Therefore, analysis of drug release from swellable matrices must be performed with a flexible model that can identify the contribution to overall kinetics, an equation proposed by Ritger and Peppas. For finding out the mechanism of drug release from floating hydrophilic matrix tablet, the dissolution data obtained from the above experiments were treated with the different release kinetic equations.

2.6 Data Analysis

The response surface methodology is a collection of mathematical and statistical techniques used for modelling and analysis of problems in which a response of interest is influenced by several variable and the objectives is to optimize this response.

The run or formulation, which are designed based on Box-Behnken design are evaluated for the response. The response values are subjected to multiple regression analysis to find out the relationship between the factor used and the response value obtained. The response values subjected for this analysis are:

1. Total floating time
2. $T_{50\%}$
3. % $CR_{10\ hrs}$
4. Diffusion coefficient (n)

The Diffusion coefficient (n) obtained after fitting the release rate to Korsmeyer and Peppas model. The multiple regression analysis was done using DESIGN EXPERT 6.0.11 (STAT-EASE) demo version software, which specially meant for this optimization process.

Analysis of data was carried out using ANOVA and the individual parameter was evaluated with F-test. Using the regression coefficient of factor, the polynomial equation for each response is generated.

2.6.1 Disintegration Test

Disintegration test are performed to ensure that the drug substance are fully absorbed and dissolved into the gastrointestinal tract. Each tube contains one tablet and the rack was placed in a 1L beaker of 37 ± 2°C. These tablets are placed below the surface of liquid and not closer then bottom of the beaker. A device called standard motor has been used to move the assembly which contains the tablets down and up through a specific distance with the frequency of 28-32 cycles per minute. Time is been noted when there is no tablet.

2.7 Floating Parameters

2.7.1 Buoyancy Lag Time

The study was based on buoyancy of tablets in100 ml of 0.1N HCl. 0.1N HCl were taken in a glass beaker of 100 ml. Put amoxicillin tablet in this beaker for observation. The floating time of tablet were observed visually. Optimized bilayer tablet the Buoyancy lag time is been reported.

2.7.2 Duration of Floating Time

A 100 ml of glass beaker containing 0.1N HCl anamoxicillin tablet was placed for observation. In duration of floatation the total duration for which tablet remains floating was recorded. Data of the floating time study and optimized bilayer tablet are shown.

2.7.3 Swelling Index

In Dissolution Testing Apparatus tablet were placed for determining the swelling properties of tablet layer. It was conducted in a container capacity of 1000 ml of 0.1N HCl at 37 ± 0.5 °C it was then rotated for 30 minutes on 50 RPM. Then the tablets were removed from the medium, to remove excess water and weighed. According to the equation, swelling characteristics were expressed in terms of percentage water uptake (WU %).

$$\text{Swelling Index} = \frac{(\text{Weight of dry tablet} - \text{weight of swollen tablet}) \times 100}{\text{Weight}}$$

2.7.4 Drug Content Determination of Amoxicillin

Randomly select twelve tablets and weighed then triturated to get the powder. Take 100 mg of amoxicillin tablet were dissolved in distilled water (50ml) and then sonicated it for 15minutes. After sonication, volume was makeup up to 100 ml

using distilled water and filtered. Sample solution were preparing for analysis by using UV-spectrophotometry at 230 nm.

2.7.5 Optimization

The computation for optimized formulation was carried using software, DESIGN EXPERT 6.0.11 (STAT-EASE). The response variable considered for optimization were total floating time, T50%, %CR10 hrs, diffusion coefficient (n).

The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors). By utilizing DESIGN EXPERT 6.0.11 (STAT-EASE) demo version software, we got one solution for optimized formulation. The optimized formulation is prepared and evaluated for total floating time, T50%, %CR10 hrs, diffusion coefficient (n). Observe response value of the optimized formulation is compared with predicted value.

2.8 Stability Studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

ICH specified the length of study and storage conditions.

2.8.1 Long-Term Testing

25°C ± 2°C / 60 % RH ± 5 % for 12 months

2.8.2 Accelerated Testing

40°C ± 2°C / 75 % RH ± 5 % for 6 months

2.8.3 Method

The optimized formulation was packed in amber-colored bottle, which was tightly plugged with cotton and capped. It was then stored at 25° C/60 % RH for 6 weeks. The formulation was evaluated for hardness, drug content, floating properties,dissolution study and compare with original formulation.

3. RESULTS

3.1 Preformulation Study

3.1.1 Identification Test Drug

A. Scanning of Amoxicillin in 0.1 N HCl, UV spectrum of Amoxicillin in 0.1 N HCl shows that the drug had λmax of 230.0 nm that was exactly similar as reported.

Table 1: λmax of Amoxicillin in Different Dissolution Medium and in Organic Solvents

S. No.	Solvents	λmax (nm)
1	Methanol + water	230
2	Methanol	230
3	Phosphate buffer	230
4	Methanol + 0.1 N HCl	230

Table 1: Amoxicillin Solubility in different solvents

S. No.	Solvents	Solubility
1	Purified Water	++
2	Methanol	+
3	Ethanol	+
4	Acetone	+
5	HCl	-

(-) Insoluble, (+) Soluble

Table 3: Melting Point of Amoxicillin

Method used	Experimental value	Literature value*
Capillary fusion method	160^0 -200^0	194°

Table 4: Partition Coefficient Values of Amoxicillin in n-Octanol: Distilled Water

Medium	Experimental value	Literature value
Double distilled water	6.9	7.14

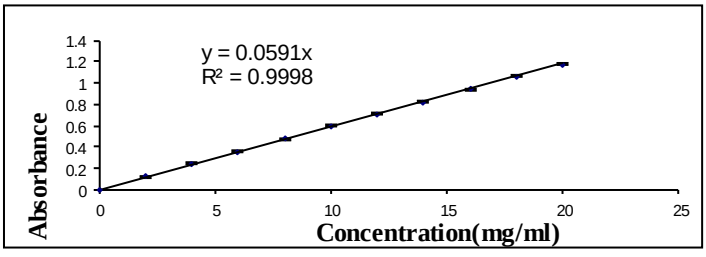

Figure 1: Standard Plot of Amoxicillin in 0.1 N HCl

Table 5: Standard curve of amoxicillin in 0.1 N HCl at 230 nm

Concentration (µg/ml)	Absorbance			
	I	II	III	Average ± SD
0	0.000	0.000	0.000	0.000 ± 0.000
2	0.124	0.124	0.121	0.123 ± 0.002
4	0.235	0.255	0.242	0.244 ± 0.010
6	0.354	0.367	0.355	0.359 ± 0.007
8	0.477	0.484	0.468	0.476 ± 0.008
10	0.602	0.616	0.585	0.601 ± 0.016
12	0.713	0.724	0.699	0.712 ± 0.013
14	0.825	0.834	0.815	0.825 ± 0.010
16	0.944	0.951	0.930	0.942 ± 0.011
18	1.062	1.071	1.057	1.063 ± 0.007
20	1.166	1.186	1.169	1.174 ± 0.011

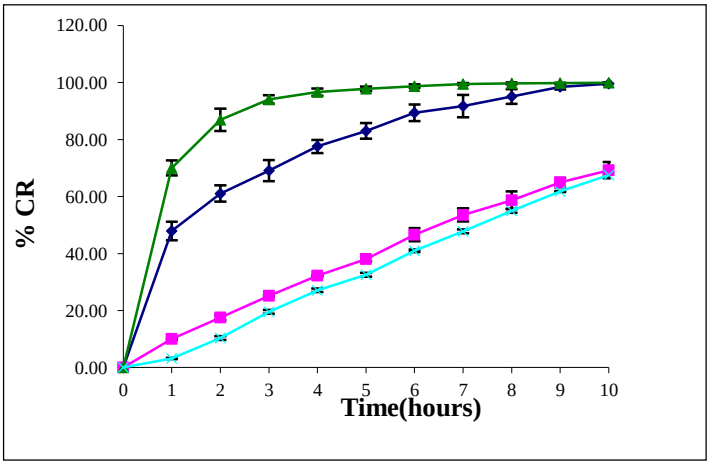

Figure 2: Dissolution Profile of Batch F1 to F9

3.2 Floating Property Study

The floating lag time and total floating time of different batch of tablets are shown in Table 10:

3.3 Dissolution Study

The *in vitro* drug release data of different batches of tablets are shown in Table 11 to Table 15. The plots of % Cumulative drug release v/s Time (hr) for tablet of different batches.

Table 6: Pre-compression parameter of blend powder of Amoxicillin

Formulation code	Bulk density(g/cm^3)	Tapped density	Angle of repose	Hausner's ratio	Carr's index (%)
F1	0.366±0.015	0.574±0.026	23±0.17	1.23±0.03	19.6±0.015
F2	0.56±0.018	0.588±0.028	25±0.12	1.27±0.022	21.8±0.012
F3	0.52±0.013	0.581±0.024	24±0.13	1.23±0.019	21.2±0.013
F4	0.45±0.014	0.584±0.023	26±0.16	1.26±0.017	17.3±0.018
F5	0.475±0.017	0.567±0.025	27±0.17	1.20±0.017	16.2±0.014
F6	0.485±0.016	0.569±0.027	25±0.13	1.19±0.019	21.1±0.012
F7	0.460±0.018	0.577±0.025	27±0.15	1.24±0.022	18.4±0.015
F8	0.461±0.014	0.598±0.035	25±0.15	1.29±0.019	19.1±0.016
F9	0.464±0.013	0.580±0.024	27±0.16	1.24±0.021	19.7±0.013
F10	0.461±0.013	0.582±0.026	28±0.17	1.25±0.021	18.2±0.015
F11	0.478±0.014	0.585±0.027	25±0.13	1.28±0.019	18.2±0.016
F12	0.462±0.018	0.575±0.029	25±0.18	1.26±0.021	21.6±0.017
F13	0.425±0.03	0.466 ±0.001	27±0.15	1.25±0.021	18.2±0.015
F14	0.56±0.018	0.574±0.026	23±0.17	1.23±0.019	21.2±0.013
F15	0.52±0.013	0.588±0.028	25±0.12	1.26±0.017	17.3±0.018
F16	0.45±0.014	0.581±0.024	24±0.13	1.20±0.017	16.2±0.014
F17	0.475±0.017	0.584±0.023	25±0.15	1.19±0.019	21.1±0.012
F18	0.485±0.016	0.567±0.025	27±0.16	1.24±0.022	18.4±0.015

Table 7: optimization parameters of amoxicillin tablets

Formulation code	Hardness (Kg/cm2)	Friability (%)	Uniformity of weight (%)	Swelling index in 1hour (%)	Buoyancy lag time (minutes)	Duration of floating (hours)	Drug content
F1	4.3±0.65	0.94	1.28±0.09	12.3	1.2±0.91	>9	98.4
F2	4.2±0.50	0.90	1.56±0.09	12.9	1.2±0.89	>9	95.3
F3	4.4±0.34	0.87	1.45±0.06	13.2	1.46±0.93	>9	96.4
F4	4.5±0.18	0.90	1.52±0.07	13.5	1.28±0.78	>9	98.2
F5	4.7±0.21	0.89	0.475±0.09	13.4	1.45±0.69	>9	98.7
F6	4.6±0.27	0.88	0.485±0.05	13.1	1.39±0.87	>9	97.45
F7	4.5±0.26	0.97	0.460±0.02	13.6	1.37±0.92	>9	94.34
F8	4.6±0.64	0.86	0.461±0.05	13.3	1.42±0.86	>9	98.56
F9	4.7±0.44	0.93	0.464±0.03	12.6	1.44±0.90	>9	98.47
F10	4.6±0.34	0.92	0.461±0.02	12.8	1.45±0.86	>9	98.68
F11	4.2±0.76	0.95	0.478±0.01	12.5	1.43±0.76	>9	98.62
F12	4.6±0.40	0.84	0.462±0.07	12.3	1.38±0.82	>9	98.55
F13	4.4±0.34	0.87	1.52±0.07	13.5	1.46±0.93	>9	98.2
F14	4.5±0.18	0.90	0.475±0.09	13.4	1.28±0.78	>9	98.7
F15	4.7±0.21	0.89	0.485±0.05	13.1	1.45±0.69	>9	97.45
F16	4.6±0.27	0.88	0.460±0.02	13.6	1.39±0.87	>9	94.34
F17	4.5±0.26	0.97	0.461±0.05	13.3	1.37±0.92	>9	98.56
F18	4.6±0.64	0.86	0.464±0.03	12.6	1.42±0.86	>9	98.47

Table 8: Formulation of Amoxicillin tablets

Preformulation number	Citric acid	Tartaric acid	Sodium bicarbonate	pH	Solubility
1	89	176	299	6.7	2
2	89	134.5	299	6.5	2
3	89	88.6	299	6.2	1
4	89	44.5	299	5.93	4
5	177	175	299	5.3	4
6	177	88.6	299	5.52	4
7	133	88.6	299	5.9	5
8	45	88.6	299	6.89	4
9	0	88.6	299	6.7	2
10	89	-	299	6.5	1
11	89	-	224.5	6.2	4
12	89	-	150	5.8	2
13	133	-	299	5.3	3
14	133	-	224.5	5.5	1
15	133	-	150	6.3	5

Table 9: Evaluation parameter of optimized bilayer tablet

Parameters	Observations
Hardness (Kg/cm^2)	4.5±0.36
Friability (%)	0.623
Uniformity of weight (%)	1.2±0.05
Swelling index in 1hour	11.2%
Buoyancy lag time (minutes)	1.47±0.80
Duration of floating(hours)	>9
Drug content (Amoxicillin)	247.7
Disintegrations Time (seconds)	**26 ± 1.2**

Table 10: Floating properties of tablets of each batch

Batch	Floating lag time (seconds)		Total floating time (hr)	
	Average	SD	Average	SD
F1	19.67	1.53	4.83	0.29
F2	1346.67	128.58	10.00	0.00
F3	13.67	1.53	3.73	0.25
F4	22.33	2.52	10.00	0.00
F5	37.00	2.65	10.00	0.00
F6	86.67	7.64	10.00	0.00
F7	11.67	1.53	03.17	0.29
F8	16.00	2.00	10.00	0.00
F9	80.33	3.06	10.00	0.00
F10	36.00	3.61	10.00	0.00
F11	25.67	2.08	10.00	0.00
F12	15.33	1.53	04.83	0.29
F13	15.33	0.58	10.00	0.00
F14	15.00	1.00	10.00	0.00
F15	15.00	1.00	10.00	0.00
F16	14.67	0.58	10.00	0.00
F17	15.33	0.58	10.00	0.00

3.4 Data Analysis

The responses were recorded and analysis of data was carried out using ANOVA (STAT-EASE). The individual parameter was evaluated using F-test and a polynomial equation for each response was generated using MLRA. The design and response summary data are represented in table 17.

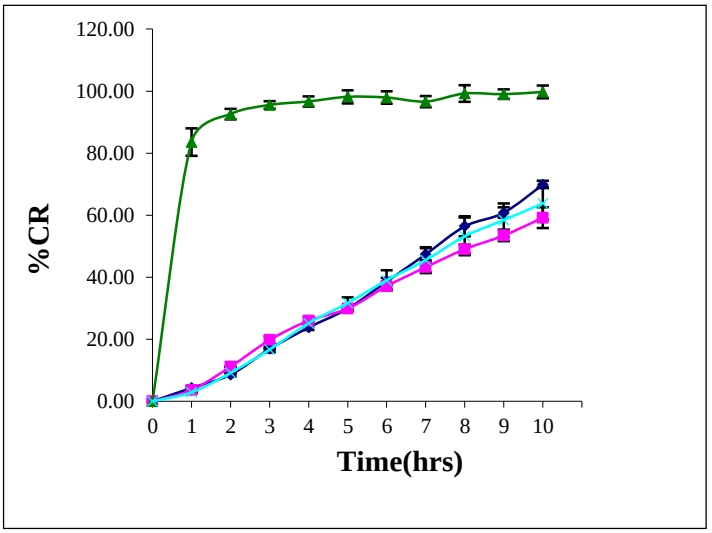

Figure 3: Dissolution Profile of Batch F5 to F8

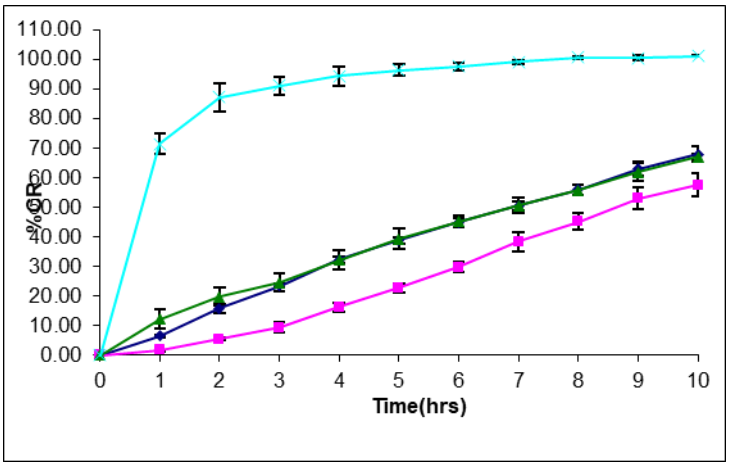

Figure 4: Dissolution Profile of Batch F9 to F12

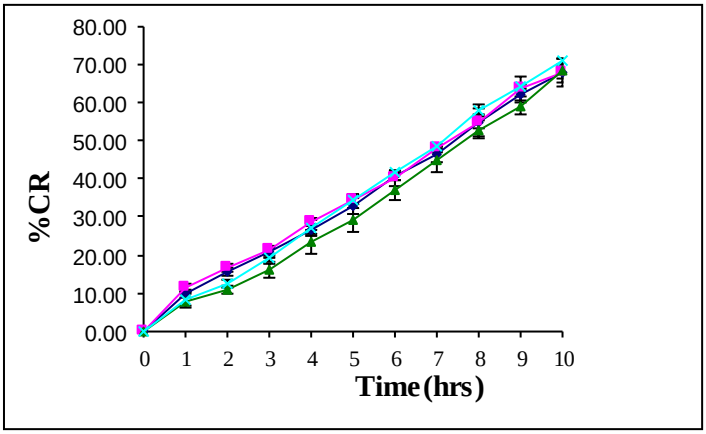

Figure 5: Dissolution Profile of Batch F13 to F16

Table 11: Dissolution data of tablets of batch F1 to batch F4

Time (hr)	Batch							
	F1		F2		F3		F4	
	%CR	SD	%CR	SD	%CR	SD	%CR	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	47.91	3.26	9.97	0.30	70.04	2.59	3.21	0.24
2	61.07	2.86	17.53	0.90	86.90	3.88	10.34	0.68
3	69.07	3.69	25.14	0.32	94.04	1.47	19.53	0.70
4	77.57	2.27	32.17	0.30	96.63	1.30	27.11	0.60
5	83.02	2.72	38.01	0.78	97.78	0.83	32.56	0.64
6	89.36	2.96	46.60	2.30	98.73	0.62	40.99	0.44
7	91.73	3.95	53.53	2.28	99.48	0.31	47.81	0.71
8	95.12	2.58	58.71	3.08	99.65	0.32	54.97	0.69
9	98.47	0.94	64.90	1.60	99.82	0.15	61.76	0.16
10	99.56	0.43	69.26	2.82	99.93	0.07	67.49	0.49

Table 12: Dissolution data of tablets of batch F5 to batch F8

Time (hr)	Batch							
	F5		F6		F7		F8	
	%CR	SD	%CR	SD	%CR	SD	%CR	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	4.29	0.40	3.58	0.24	83.59	4.41	2.87	0.17
2	8.57	0.66	11.15	0.00	92.58	1.71	9.14	0.26
3	16.86	0.23	19.74	1.15	95.53	1.20	16.65	0.93
4	23.78	0.78	25.99	1.13	96.66	1.63	25.16	0.30
5	29.88	0.58	29.88	0.48	98.15	2.09	31.65	1.85
6	38.60	1.22	37.12	0.86	97.93	1.99	38.99	3.30
7	47.41	1.94	43.25	1.58	96.63	1.79	45.50	4.13
8	56.42	3.24	49.06	1.41	99.23	2.71	53.16	6.06
9	60.83	1.72	53.49	1.87	99.00	1.54	58.39	5.42
10	69.91	1.19	59.19	3.39	99.73	2.09	63.75	5.25

Table 13: Dissolution data of tablets of batch F9 to batch F12

Time (hr)	Batch							
	F9		F10		F11		F12	
	%CR	SD	%CR	SD	%CR	SD	%CR	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	6.57	0.46	1.67	0.09	12.17	3.22	69.35	8.02
2	15.75	1.37	5.42	0.38	19.70	3.01	87.13	4.75
3	23.43	0.69	9.35	1.60	24.57	3.17	90.92	2.95
4	32.30	1.06	16.18	1.45	32.17	3.21	94.17	3.10
5	38.80	1.14	22.75	1.43	39.30	3.53	96.29	1.92
6	44.88	1.54	29.76	1.70	45.00	1.97	97.48	1.40
7	50.48	1.51	38.28	3.30	50.52	2.48	98.99	0.83
8	55.81	1.89	45.12	2.88	55.76	1.82	99.89	0.75
9	62.79	2.41	52.96	3.64	61.81	3.13	99.91	1.30
10	67.93	2.47	57.35	3.89	66.90	1.18	99.97	0.65

Table 14: Dissolution data of tablets of batch F13 to batch F16

Time (hr)	Batch							
	F13		F14		F15		F16	
	%CR	SD	%CR	SD	%CR	SD	%CR	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	9.91	0.31	11.39	0.93	7.71	1.18	8.48	2.23
2	15.70	1.07	16.67	1.07	10.94	1.16	12.39	1.10
3	20.54	1.08	21.10	1.17	16.05	1.82	19.39	1.14
4	26.60	1.49	28.66	1.10	23.29	3.15	27.23	1.72
5	32.85	2.27	34.51	1.35	29.25	3.11	34.36	0.88
6	40.49	0.79	40.12	1.89	37.08	2.41	41.78	0.69
7	46.56	1.97	47.95	0.83	44.64	2.80	48.54	0.66
8	54.79	1.52	54.96	3.65	52.86	2.47	58.19	1.38
9	62.14	1.66	63.48	3.15	59.14	2.39	64.03	0.75
10	67.85	1.47	67.92	3.80	68.49	3.10	70.91	0.83

Table 15: Dissolution data of tablets of batch F17

Time (hr)	Batch	
	F17	
	%CR	SD
0	0.00	0.00
1	11.71	2.92
2	17.86	3.02
3	22.01	2.84
4	28.47	2.36
5	37.48	6.51
6	44.59	8.51
7	51.54	9.02
8	58.88	8.68
9	65.34	8.74
10	70.15	4.96

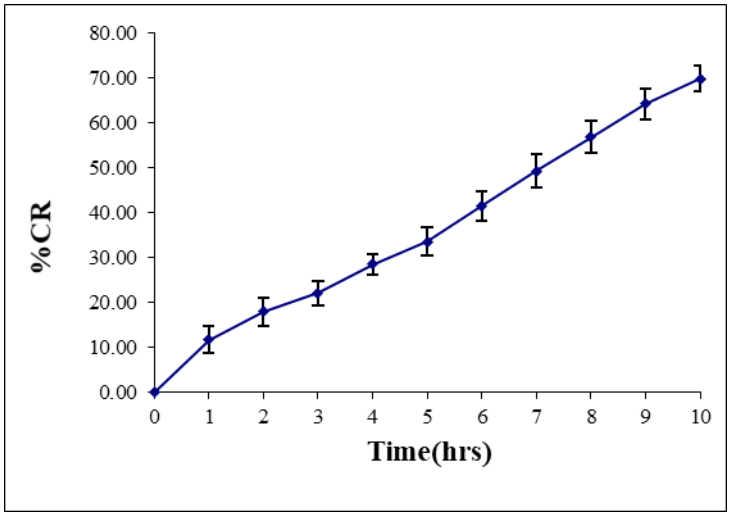

Figure 6: Dissolution Profile of Batch F17

3.5 Optimization

The optimized formulation obtained by applying constrains is shown in Table 18 and was prepared and evaluated for total floating time, $T_{50\%}$, $\%CR_{10\ hrs}$, diffusion coefficient (n). Optimized formulation had minimum floating lag time i.e. 20 ± 3 seconds and total floating time was found to be 10 hours or maximum. Dissolution data of optimized formulation are shown in Table 19 and dissolution profile of optimized formulation is shown in Figure 7.

3.6 Treatment of Dissolution Data

The data obtained after dissolution was subjected to zero order kinetic equation, Higuchi equation and korsmeyer and peppas equation. Percentage Error of optimized formulation for TFT was found to be more. However other responses exhibit negligible values of % Error. The predicted and observed values with % error of optimized formulation for the responses total floating time, $T_{50\%}$, $\%CR_{10\ hrs}$, diffusion coefficient (n) are displayed in Table 20.

3.7 Stability Studies

Stability study for optimised formulation were performed for 6 weeks. The condition maintain was 25°C/60 RH. After 6 week, optimised formulation was evluated for hardness, drug content, floating properties, and dissolution study. Comparision of properties is shown in Table 22

Table 16: Dissolution data treatments of tablets of batch F1 to batch F17

Batch	Zero order		Higuchi		KorsmeyerPeppas		
	K_0	r^2	K_H	r^2	N	r^2	K_m
F1	12.789	0.3335	35.193	0.9258	0.324	0.9952	48.65
F2	7.376	0.9880	19.331	0.9133	0.856	0.9992	9.84
F3	13.187	-0.6216	39.456	0.5383	0.138	0.8341	76.09
F4	6.765	0.9951	17.450	0.8356	1.285	0.9842	3.96
F5	6.695	0.9859	17.148	0.7977	1.243	0.9966	4.10
F6	6.051	0.9957	15.710	0.8674	1.166	0.9791	4.50
F7	13.971	-0.9879	36.660	0.3385	0.066	0.8534	86.66
F8	6.417	0.9925	16.520	0.8261	1.328	0.9875	3.45
F9	7.130	0.9903	18.690	0.9015	0.989	0.9907	7.45
F10	5.393	0.9586	13.650	0.7377	1.558	0.9977	1.76
F11	7.130	0.9730	18.789	0.9376	0.751	0.9965	11.65
F12	13.947	-0.5441	39.256	0.5770	0.146	0.8911	74.59
F13	6.801	0.9963	17.684	0.8716	0.857	0.9873	8.83
F14	6.913	0.9929	18.033	0.8859	0.806	0.9816	9.92
F15	6.473	0.9896	16.640	0.8134	1.000	0.9778	6.24
F16	7.040	0.9974	18.228	0.8468	0.975	0.9875	7.26
F17	7.282	0.9923	19.015	0.8926	0.814	0.9827	10.33

Table 17: The design and response summary data

Std	Factors			Response			
	A: Amt of HPMC	B: Amt of $NaHCo_3$	C: Amt of Citric Acid	TFT hrs	$\%CR_{10\ hr}$	$T_{50\%}$ hrs	N
1	50.00	20.00	05.00	5.83	99.56	1.2	0.324
2	90.00	20.00	05.00	10.00	69.26	6.4	0.856
3	50.00	50.00	05.00	04.73	99.93	0.7	0.138
4	90.00	50.00	05.00	10.00	67.49	7.3	1.285
5	50.00	35.00	00.00	10.00	69.91	7.2	1.243
6	90.00	35.00	00.00	10.00	59.19	8.2	1.166
7	50.00	35.00	10.00	04.17	99.73	0.6	0.066
8	90.00	35.00	10.00	10.00	63.75	7.6	1.328
9	70.00	20.00	00.00	10.00	67.93	6.8	0.989
10	70.00	50.00	00.00	10.00	57.35	8.6	1.558
11	70.00	20.00	10.00	10.00	66.90	8.6	0.751
12	70.00	50.00	10.00	05.83	99.93	0.7	0.146
13	70.00	35.00	05.00	10.00	67.85	7.4	0.857
14	70.00	35.00	05.00	10.00	67.92	7.3	0.806
15	70.00	35.00	05.00	10.00	68.49	7.6	1.000
16	70.00	35.00	05.00	10.00	70.91	7.2	0.975
17	70.00	35.00	05.00	10.00	70.15	7.0	0.814

Table 18: Optimized formulation

Ingredients	*Quantity*
Drug (mg)	50.00
HPMC (mg)	52.93
$NaHCO_3$ (mg)	24.79
Citric Acid (mg)	01.32
Mg Stearate (mg)	07.00
Lactose (mg)	88.96

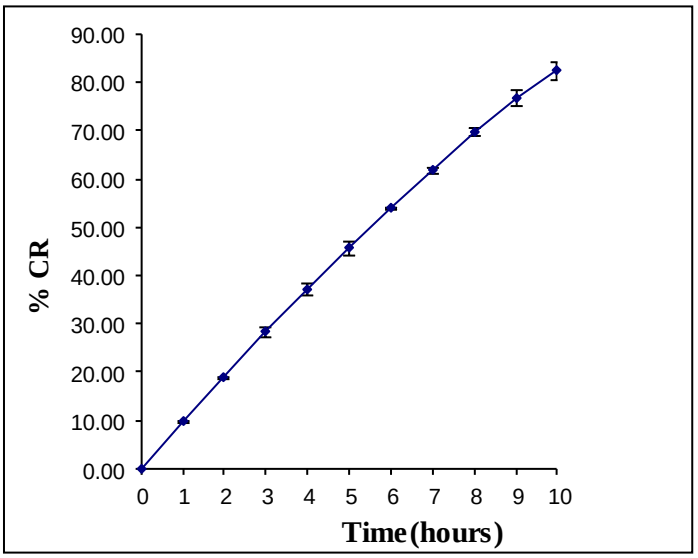

Figure 7 : Dissolution profile of optimized formulation

Table 19: Dissolution data of optimized formulation

Time(hrs)	0	1	2	3	4	5	6	7	8	9	10
% CR ± SD	00.00 ± 0.00	09.80 ± 0.18	18.82 ± 0.24	18.82 ± 0.24	37.01 ± 1.28	45.61 ± 1.60	53.89 ± 0.22	61.74 ± 0.72	69.69 ± 0.82	76.80 ± 1.74	82.37 ± 1.76

Table 20: Treatment to dissolution data of optimized formulation

Zero order		**Higuchi**		**KorsmeyerPeppas**		
K_0	**R^2**	**K_H**	**r^2**	**n**	**r^2**	**K_m**
8.66	0.9942	28.12	0.9406	0.9336	0.9992	0.99

Table 21: Comparison between observed values and predicted values of optimised formulation

Response	**Observed**	**Predicted**	**% Error**
Total floating time	10 hours	8.8	12.00
$T_{0.5}$	5.3 hours	5.0	5.66
% CR_{10hrs}	82.37	80.22	2.62
Diffusion coefficient(n)	0.93	0.91	2.15

Table 22: Evaluated data at 0 and 6th week

Parameter	**0 week**	**6th week**
Hardness	3 kg	3 kg
Drug content	49.89 ± 0.48 mg	49.50 ± 0.39 mg
Floating lag time	20 ± 3 seconds	21 ± 2 seconds
Total floating time	10 hours	10 hours

4. DISCUSSION

On the basis of preliminary identification test it was concluded that the drug complied the preliminary identification. There was a no drug excipients interaction was confirmed by the drug and physical mixture. The viscosity of HPMC (2% w/v) in water was found to be 4100, which would sufficient to maintain the integrity of the matrix. The free-flowing nature of drug and excipients was clearly evident from the values of Carr's index and Hausner ratio. The value also suggested the suitability of the mixture to be processed as a directly compressible material in formulation of tablets of amoxicillin. The physical parameters of

tablets showed that the tablets of all batches had desirable physical characteristics.

The results of floating lag time are shown in Table. All the batches of tablet produced were found to exhibit short floating lag times. The short floating lag time can be due to presence of sodium bicarbonate and citric acid. Sodium bicarbonate and citric acid were used in combine to minimize the lag time in fabrication of GRDFs. The tablet of batch F2 exhibited a longer floating lag time of 23 minutes. This can be due to the presence of $NaHCO_3$ at low level and HPMC at high level. The high level of HPMC would possibly prevents the entry of media into the tab matrix and prolong the floating lag time. The effect of concentration of HPMC on floating has been reported in literature.

The results of total floating time (TFT) are shown in Table. All batches of tablet were found to exhibit maximum floating time i.e. 10 hours. Tablets of batch F1, F3, F7 and F12 exhibited short floating time i.e. 3-5 hours because they eroded faster in media due to high amount of $NaHCO_3$ and Citric acid in coupled with less amount of HPMC. Value of "Prob > F" less than 0.05. One factor plot shows that amount of HPMC increased, TFT increased due to increased matrix integrity at high amt of HPMC while amt of $NaHCO_3$ and citric acid increases, TFT decrease because $NaHCO_3$ and citric acid promote faster erosion of tablets.

So, the presence of optimum amount of HPMC, $NaHCO_3$, and citric acid is important in achieving good floating time and minimum floating lag time. The finding also supported by study of Baumgartner et al. who reported that incorporation of sodium bicarbonate helps to improve floating properties by reacting with gastric fluid when dosage form comes in contact with media. These produce carbon dioxide gas which entrapped inside the hydrophilic matrices leads to increase in volume of dosage form resulting in lowering of density and dosage form starts to float.

The relationship between the dependent and independent variables was further elucidated using contour and response surface plots. Contour plot shows that at a fixed level of $NaHCO_3$, TFT decrease from 10 to 5.14 hrs at low level of A (HPMC) and high level of C (citric acid). However, at high level of A (HPMC) TFT remains unaffected with change in amount of citric acid. These might be due to a low level of HPMC (50mg), matrix unable to remain intact with increase in citric acid. The interaction effect of B ($NaHCO_3$) and C (citric acid) at a fixed level of A (70mg) was shown. The TFT decreases at high levels of B and C whereas at low levels, TFT remains high unaffected to change each other.

The dissolution data of tablet formulation are shown in Table 11-15 and % CR vs. time plot is shown in Fig 2-6. It was clear from dissolution profiles that the tablets of batch F3, F7, and F12 exhibits initial burst phase during the first hour of dissolution. The burst phase was followed by a limited drug release for the rest of the period. The initial burst release can be attributed to low levels of HPMC combined with high levels of $NaHCO_3$ and citric acid. It was observed during the dissolution studies that tablets of all three batches eroded quickly with increased effervescence. Similar kind of quick erosion of tablet matrix was observed with high level of $NaHCO_3$ and citric acid in the formulation of floating tablet of calcium carbonate. Other formulation showed a linear pattern of Amoxicillin release from floating tablet.

Time required for 50 % drug to get released ($T_{50\%}$) and $\%CR_{10hrs}$ were found to be in the range of 0.7 to 8.6 hours and 57.35 ± 3.89 to 99.93 ± 0.07 respectively. Value of "Prob > F" less than 0. 05. It was shown that as the amount of polymer increased, $T_{50\%}$ of formulations increased, whereas $\%CR_{10hrs}$ decrease. It was noticed that the matrix became more intact which slowed down the water uptake resulting in poor water diffusion and poor drug release. As the amount of citric acid increased, it reacted with $NaHCO_3$ producing effervescence and rendering the matrix more porous. This resulted in an increased $\%CR_{10hrs}$ and decrease $T_{50\%}$ from the porous tablet matrix.

Response surface plots and Contour plot indicated that at a fixed level of B (35 mg) and low level of A (amount of HPMC), % CR_{10hrs} increases from 68.11 to 90.00 % and $T_{50\%}$ decrease from 6.86 to 1.66 as the amount of citric acid (C) increases from 0 to 10 mg. However simultaneous increasing amount of HPMC and amount of citric acid had no significant effect on % CR_{10hrs} and T 50%. The interaction effect of B ($NaHCO_3$) and C (amount of citric acid) at a fixed level of A (70mg) indicated that % CR_{10hrs} increases whereas $T_{0.5}$ decrease at high levels of both B and C. this can be attributed to formation of compact matrix with increasing level of HPMC and porous matrix with increasing level of $NaHCO_3$ and citric acid.

The dissolution data treatment of different batches of tablet is shown in Table. The dissolution data of most of formulation fitted well into zero order release kinetics. The data fitment of the dissolution profiles done according to Korsmeyer, Peppas model indicating the values of diffusion coefficients obtained range from 0.06 to 1.55. The formulation F1, F3, F7 and F12 which exhibited an initial burst phase showed a low value of diffusion coefficients ranging from 0.06 to 0.32. Low level of HPMC coupled with high amount of $NaHCO_3$ and citric acid for these formulations were responsible for the incompatibility of the system to control the release of Amoxicillin from the GFDDS. Other tablet formulation gave relatively higher in value for diffusion coefficient ranging from 0.75 to 1.55. The mechanism of drug release in these cases was known to follow case II transport mechanism i.e. characterized by both erosion and diffusion.

The ANOVA for the diffusion coefficient (n) of the formulations demonstrates that Values of "Prob > F" were less than 0.05. indicating the factor, A, C, AC, BC had significant effect on diffusion coefficient (n). One factor plot shows that as HPMC level increased, the drug delivery system gained more control over the release of Amoxicillin, resulting in an increased diffusion exponent value. Citric acid was found to exert an opposite effect on the diffusion coefficient, which is clearly evident from the negative value for the regression coefficient in polynomial equation. An increased amount of citric acid could cause a decrease in value of diffusion exponent (n) by initiating the formation of porous matrix tablet. An optimum amount of citric acid in delivery device could be maintained without compromising drug release by precisely monitoring the levels of $NaHCO_3$ and HPMC.

For the optimization of floating tablets of Amoxicillin constraints was fixed for all factors and response. Constraints were set according to formulation of floating tablets using minimum amt of excipients, which will give desired response values. In the present study our aim was zero order drug release from the tablets and so that the diffusion coefficient was targeted to 1.

The optimized formulation was prepared after applying above criteria and observed response values was compared with predicted values. Comparison chart of observed and predicted values is shown Table 24. The predicted values of TFT had indicated that tablet would erode in 8.8 hours. But during dissolution study it was observed that a very small tablet was there at end of study and this will lead to high % error. However other responses exhibit negligible values of % Error.

The dissolution data of optimized formulation fitted well into zero order release kinetics and Korsmeyer Peppas model. The regression values and diffusion coefficients (n) values 0.91 i.e. nearest to 1 indicated that floating tablets follow zero order kinetics of drug release. The mechanism of drug release in these cases was known to follow case II transport mechanism i.e. characterized by both erosion and diffusion.

Stability study was performed for optimized formulation and it was found that formulation was stable for 6 week at 25 °C/ 60% RH. The formulation was found to be stable in terms of morphology, drug content and drug release.

5. CONCLUSION

Gastric retention time of amoxicillin can be increased by formulating it in a floating dosage form using optimum amount of HPMC, NaHCO3 and citric acid. The produced tablets exhibited good floating time and controlled drug release over a period of 10 hours. It was concluded that the floating tablets released drug in stomach in view to enhance bioavalability of amoxicillin.

It can be concluded that by the application of optimization technique, optimized formulation can be obtained with minimum expenditure time and money.

It can be concluded that a floating tablet with good flow property and controlled release property can be obtained by optimizing amount of HPMC, NaHCO3 and citric acid. The number of experimental trials carried out to produce the optimized formulation was considerably reduced thereby substantially cutting down the expenditure on time and money.

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