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Formulation and Evaluation of a Floating tablet of Amoxicillin and Metronidazole

Brijesh Kumar*, Raju Choukse, Rakesh Patel and Revathi A. Gupta

Dr. A. P. J. Abdul Kalam University, Indore (M.P.) - India

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Abstract

Two ideal rationales of this project are namely, spatial placement and temporal delivery of a drug. Combination of amoxicillin and metronidazole has higher eradication of *H. pylori*. Amoxicillin is a drug having tendency to degrade in alkali, it decompose first by opening the lactame to its penicilloic acid. Floating tablet would put advantage to release drug only in acidic medium that would protect amoxicillin to expose in alkali.In this research first of all a noneffervescent floating drug delivery was used to achieve in vitro buoyancy. In the initial batches tablets prepared using polymers such as HPMC K100M, guar gum and xanthan gum did not exhibit sufficient swelling o provide in vitro buoyancy. An effervescent approach was then adopted. Three batches (A1 to A3) were prepared using HPMC K 100M, guar hum, and xanthan gum, respectively; sodium bicarbonate was added as a gas generating agent. Sodium bicarbonate induced CO_2 generation in the presence of dissolution media. The gas generated was trapped and protected within the gel formed by hydration of polymer, thus decreasing the density of the tablet. As the density of tablet falls below 1, the tablet becomes buoyant. Batches A2 and A3, containing guar gum and xanthan gum, failed to form a gel with sufficient strength, entrapping CO_2 gas and imparting stable and persistent bouncy.

To study the effect of sodium bicarbonate concentration on floating lag time batches A4 was formulated. The results demonstrate that as the amount of sodium bicarbonate decreases, the floating lag time increases and total floating time decreases. Thus sodium bicarbonate (100mg) was essential to achieve optimum in vitro buoyancy. Fed condition and presence of *H. Pylori* elevate pH of stomach so citric acid was incorporated in formulation to provide an acidic medium for sodium bicarbonate. However, adding citric acid to formulation might enhance dissolution, stearic acid was incorporated in the formulations to sustain release. Decreasing concentration of stearic acid in formulations (A9 to A12), raised drug release profile and decreased total floating time of tablets. Only one batch, A9, showed sufficient drug release (11 hours) but it could float only for the 10 hours.Finally batch A8 formulated with higher quantity of citric acid compared to A9, which improved total floating time of tablet, from 10 to 11 hours. Both batches (A8, A9) released drugs in almost same time (11 hours) but floating time was improved in batch A8 compare to A9 due to raised quantity of citric acid.

Keywords: Floating Tablet, Amoxicillin, Metronidazole, and temporal delivery of a drug

Introduction

Helicobacter Pylori is a gram-negative rod that colonized the mucus on the luminal surface of the gastric epithelium and identified as a causative factor in etiology of peptic ulcer disease. No single antibiotic has been able to eradicate this organism effectively due to development of resistance; therefore multiple drugs therapy is needed for patients[1-2].

Although WHO guideline suggests various drugs for eradication of *Helicobacter Pylori* and treatment of peptic ulcer but these drugs contain following limitations in conventional dosage forms:

i. Treatment of *H. pylori* may have acquired resistance to the commonly uses antimicrobial agents.
ii. As bacterium penetrates the gastric mucus layer and fixes itself to various phospholipids and glycolipids on the epithelial surface, therefore it is difficult for drug to access, both from lumen of stomach and from the gastric blood supply.

***Corresponding Author**

iii. The effective concentration of antibiotic are not delivered to the side of infection by the conventional dosage form.

Two ideal rationales of this project are namely, spatial placement and temporal delivery of a drug. Spatial placement relates to targeting a drug to a specific organ so floating tablet would target both antibiotics to the pyloric region where bacterium penetrates the gastric mucus layer and fixes itself to various phospholipids and glycolipids on the epithelial surface, otherwise it is difficult for drug to access from the gastric blood supply. Temporal delivery refers to the controlling the rate of drug delivery to the target tissue so that would be achieved by use precise polymers and effervescent system in formulation. An appropriately designed sustained release drug delivery system can be a major advance toward achieving these two rational.

Combination of amoxicillin and metronidazole has higher eradication of *H. pylori*. Amoxicillin is a drug having tendency to degrade in alkali, it decompose first by opening the lactame to its penicilloic acid. Floating tablet would put advantage to release drug only in acidic medium that would protect amoxicillin to expose in alkali. Half life of amoxicillin is less which required frequent dosing to maintain constant therapeutic levels as described and if dosing interval of drug is not appropriate large "peaks" and "valleys" in the drug blood level may result. This problem can be overcome by preparation a floating tablet with sustain release of amoxicillin which may provide constant therapeutic level rather than the peak and valley. Preparation of floating tablet would require less quantity of dose compare to conventional tablet because of local action and controlled release that would be not only patient compliant but would be economic as well because it would required less quantity of API.[3-5]

Material and Methods

Following Drugs & materials are used in this method.

Metronidazole, Amoxicillin, HPMC 100M, Guar gum, Xanthum gum, Sodium bicarbonate, Stearic acid, Citric acid

Formulation of floating tablets

Fabrication of tablet for In vitro studies:

For study purpose, 12 formulation with different excipients were prepared as shown in table 1. Talc (1% w/w) and Magnesium stearate (1% w/w) were added as a glidant and lubricant respectively. Mixture then passed thought the sieve for purpose of uniformity of particle and remaining particles again triturated and mixed. Floating tablets were prepared by direct compression method. Tablets were compressed using 10 mm die/punch set in a single punch with hand operated tablet compression machine (Lab Tech. instruments).[6-9]

Table 1: Quantities of ingredients for different batches

Ingredients (mg)	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
Metronidazole	300	300	300	300	300	300	300	300	300	300	300	300
Amoxicillin	300	300	300	300	300	300	300	300	300	300	300	300
HPMC 100M	180	-	-	180	180	180	180	180	180	180	180	180
Guar gum	-	-	180	-	-	-	-	-	-	-	-	-
Xanthum gum	-	180	-	-	-	-	-	-	-	-	-	-
Sodium bicarbonate	100	100	100	50	100	100	100	100	100	100	100	100
Stearic acid	-	-	-	-	100	50	40	30	30	20	20	10
Citric acid	-	-	-	-	40	40	30	30	20	30	20	20

Fabrication of tablet for In vivo studies

To study the in vivo fate, the tablets were prepared by incorporating barium salphate (radiopaque substance). Barium sulphate has high relative density and poor floating property. For in vivo tests tablets prepare with the composition prescribed on table 2. Talc (1% w/w) and Magnesium stearate (1% w/w) were added as a glidant and lubricant respectively. Mixture then passed thought the sieve for purpose of uniformity of particle and remaining particles again triturated and mixed. Floating tablets were prepared by direct compression method. Tablets were compressed using 10 mm die/punch set in a single punch by hand operated single punch machine.

Table 2: Formulation of tablets for in vivo studies

Ingredients	Quantity
Amoxicillin	150 mg
Metronidazole	150 mg
Barium Sulpahte	300 mg
HPMC 100 M	180 mg
Sodium bicarbonate	100 mg
Stearic acid	30 mg
Citric acid	30 mg

Evaluation of floating tablet

The prepared tablets were evaluated as per the pharmacopial parameter as well as for some more parameters , which require special concern or need to be modified, are also discussed here.

General characteristics: Light yellow, biconvex tablet with beveled edges having around 11mm diameter.[10-15]

Weight variation Test: To study weight variation, 20 tablets of each formulation were collected randomly during compression and weighed using an electronic balance to obtain average weight of each tablets. Also the individual tablet was weighted.

Limit: Weight of all individual tablets should be in the limit of average wt ±5%.

Crushing Strength: A significant strength of floating tablet is difficult to achieve because it affect the floating lag time. The limit for floating tablet is usually kept in a lower range to facilitate less lag time and release of effervescent system. The rushing strength of the tablet was measured using conventional hardness testers[70].

Friability: This test was carried out by using Tablet Friability test apparatus (Scientific). Ten preweighed tablets were rotated at 25 rpm for four minutes. The tablets were then reweighed after removal of fines (using no. 60 mesh screen), and the percentage of weight loss was calculated.

Drug Content: 10 tablets from each batch were pulverized and three samples equivalent to 250 mg of combined drugs were transferred separately to a beaker containing 100 ml of 0.1 N HCl and allowed to dissolve. An aliquot was filtered; 4 ml of the filtrate was taken to volumetric flask (100 ml) and volume made up to 100 ml with mobile phase (phosphate buffer solution (pH 4.7; 0.05 M)–methanol (95:5 v/v)) and sample (20µg/ml) was analyzed at 254 nm using HPLC.

In vitro Buoyancy studies: The time, the tablet took to emerge on the liquid (0.1 N HCl) surface (floating lag time) and the time for which the tablets remain in floated condition on the water surface (total floating time) were evaluated. The measurements were carried out for each series of tablets. The in-vitro buoyancy and floating lag time study was carried out as per the method described. The tablets were placed in a 250-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Hydration and erosion studies: The formulation capacity for hydration (dissolution medium uptake) and their extent of erosion were evaluated gravimetrically. For each time point, two tablets of each formulation were weighed (original weight) individually and exposed to 900 ml 0.1 N HCl medium under conditions similar to the dissolution test. At specific time points, tablets were removed from the medium, patted gently with a tissue paper, weighed (wet weight), dried at 60^0C for 24 hours, allow to cool and finally weighed (final dry weight). Percent weight gain (hydration) and % mass loss (erosion) were calculated according to the following equations using original, wet and dry weight values obtained from the testing.

Drug release testing: In-vitro release studies were carried out in the dissolution test apparatus USP Type II. The tests were carried out in 900 ml of 0.1N HCl for 13 hrs at 50 rpm at 37±0.5°C[73]. 5 ml of the aliquot were withdrawn at different predetermined time intervals of one hour and filtered. 1 ml of the filtrate was taken to 5 ml with mobile phase and sample (20µg/ml) was injected

in HPLC and analyzed at 254 nm using photodiod array detectors. 5 ml of 0.1N HCL was replaced in the dissolution vessel after each withdrawal to maintain sink condition. Peak area obtained from the HPLC graph was used to detect percentage drug release and mean of three batches would calculate for each batch.

In vivo buoyancy studies: One healthy human volunteer, weighing 79 k.g., was used throughout the study. In experiment, volunteer human was fasted for 24 hours and the first radiograph was made to ensure the absence of radiopaque material in the stomach. Than the tablet was administered orally with 200 ml of water. During the experiment the volunteer was at fasted condition, but water was allowed. The in vivo test was performed at pathological clinic, classic diagnostic center, Indore, with a physician, which is authorized person to perform this type of imaging.

The X ray photograph were taken of abdomen after predetermined time using X-rays machine (General Electric corporation, India). The distance between X ray machine and the object was similar for each image. This allowed us to see tablet in the body of stomach, pyloric part of stomach so the observation of tablet movements could be made. The first picture was taken 30 minutes after the administration of the tablet and then every 30 minutes for 2 hours followed by 1 h intervals until the tablet disappeared from the stomach.

Results and Discussion

Preformulation studies

Identification of drugs FTIR Spectra

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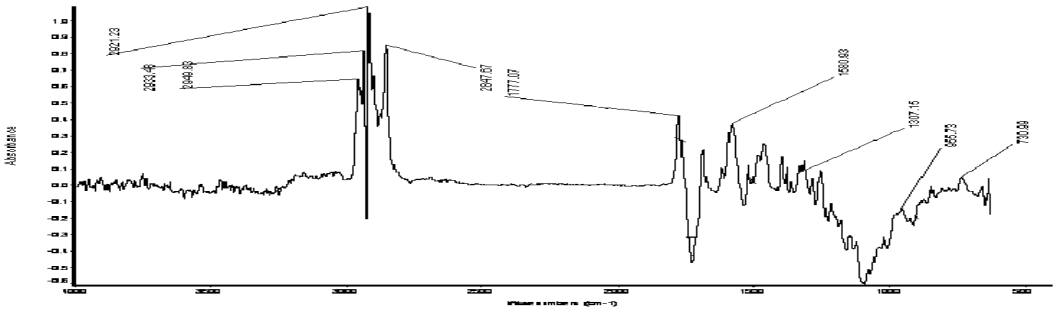
FTIR Analysis report
Date: 13/5/07 **Time: 11:35**
Title: Sample of pure amoxicillin.

Instrument detail		**Other details**	
Make :	Thermo Nicolet Coration, USA	Temperature :	30.2 °c
Model :	IR 200	% RH :	28%
Laser :	Class II IR Diode Laser	No. of scans :	24
Accessory :	Attenuated Total Reflectance	Resolution :	04
Software :	EZ OMNIC (S/W), Package, Version 6.2	Correction :	ATR



Interpretation of FTIR data

Wave number (cm^{-1})	**Assignment**
3230	OH stretch
3105	C=CH; C-H Stretch
1538	NO_2; N-Stretch
1078	C-OH; C-O Stretch
830	C-NO_2; C-N Stretch

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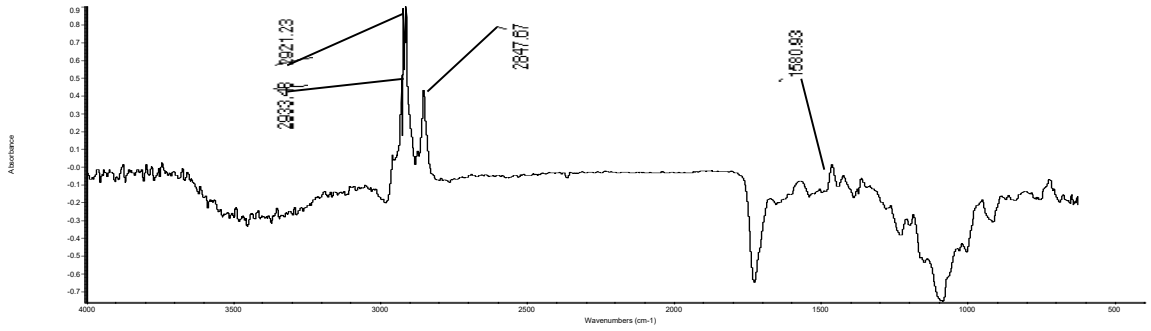
FTIR Analysis report
Date: 13/5/07 **Time: 12:35**
Title: Sample of pure metronidazole.

Instrument detail		**Other details**	
Make :	Thermo Nicolet Corporation, USA	Temperature :	30.2 °c
Model :	IR 200	% RH :	28%
Laser :	Class II IR Diode Laser	No. of scans :	24
Accessory :	Attenuated Total Reflectance	Resolution :	04
Software :	EZ OMNIC (S/W), Package, Version 6.2	Correction :	ATR



Interpretation of FTIR data

Wave number (cm^{-1})	**Assignment**
3550-3400	OH stretch
1776	ß-lactum C=O stretching
1078	Amide I C=O stretching
1582	COO- asymmetric stretching
1519	Aromatic ring

From the results of IR spectrum and Light absorption amoxiciilin and metronidazole was identified as per Pharmacopoeal specification.

UV Spectroscopy

Solution of metronidazole in 0.1 N sulfuric acid in methanol shows absorption maxima at 274 nm. Solution of amoxicillin in 0.1 N HCl shows maxima at 229 nm.

The FTIR and UV spectroscopic analysis reveals that the drugs were pure and it complies with the standards material in the Indian Pharmacopeia.

Drug-drug and drug –excipient interaction studies:

Physical and chemical incompatibility of amoxicillin and metronidazole together and with different excipients was tested using FTIR spectroscopy.

The FTIR spectra (fig. 6) shows that there was no changes in peak of amoxicillin with all excipient but there are some minor changes in the peak in the range of 2800-3500cm^{-1}in spectra of metronidazole with xanthan gum (fig. 7) which indicates that there may be some physical interaction related to the formation of weak to medium intensity hydrogen bonding between polymers. Although changes in peaks of this areas occur simply due to mixing of components without any physical or chemical interaction, but HPLC detection of this sample did not ruled out any interaction because there was separate peak for both drugs. However no major changes were drawn based on the results of FTIR. No incompatibility between metronidazole (fig. 8), amoxicillin, HPMC K100M, guar gum, xanthum

gum, sodium bicarbonate, citric acid and stearic acid was not found.

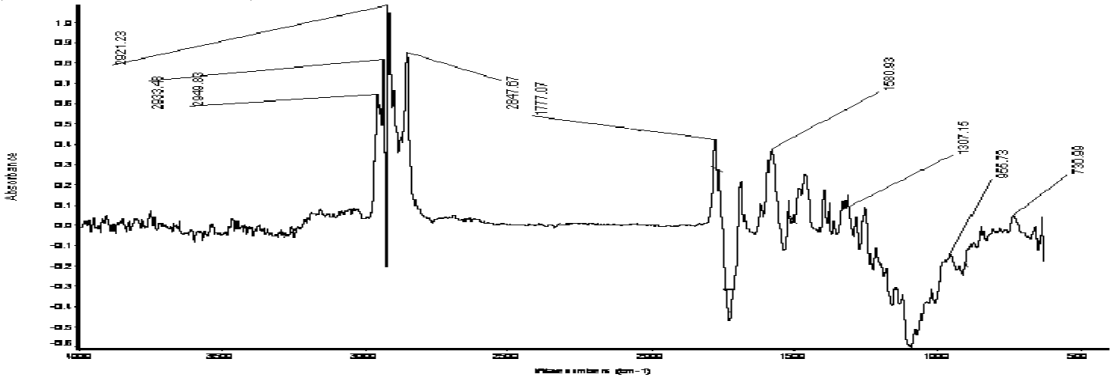


Figure 6. FTIR spectra of amoxicillin and all excipient

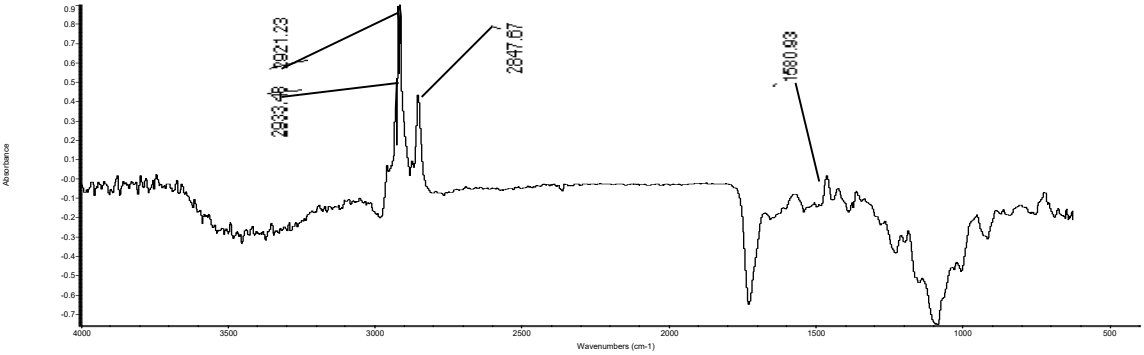


Figure 7.FTIR spectra of metronidazole and Xanthan gum

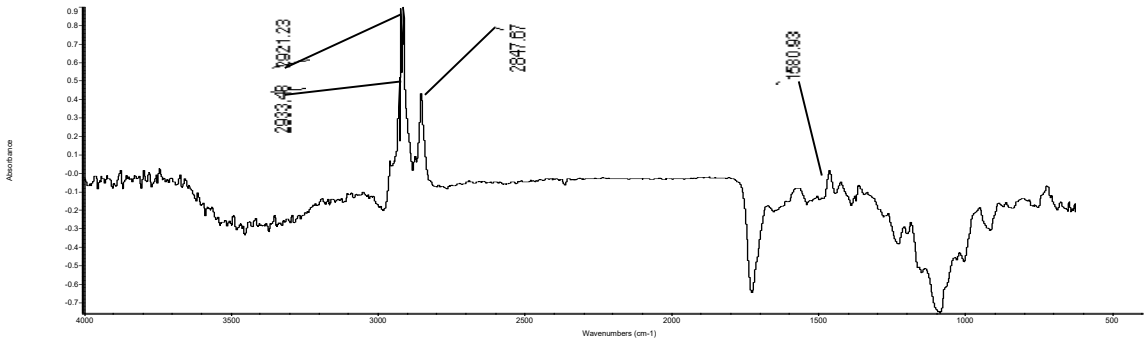


Figure 8. FTIR spectra of metronidazole with all excipients except Xanthan gum

FTIR spectra were recorded to assess drug-drug interaction. Results of FTIR spectra do not show any interference between both drugs.

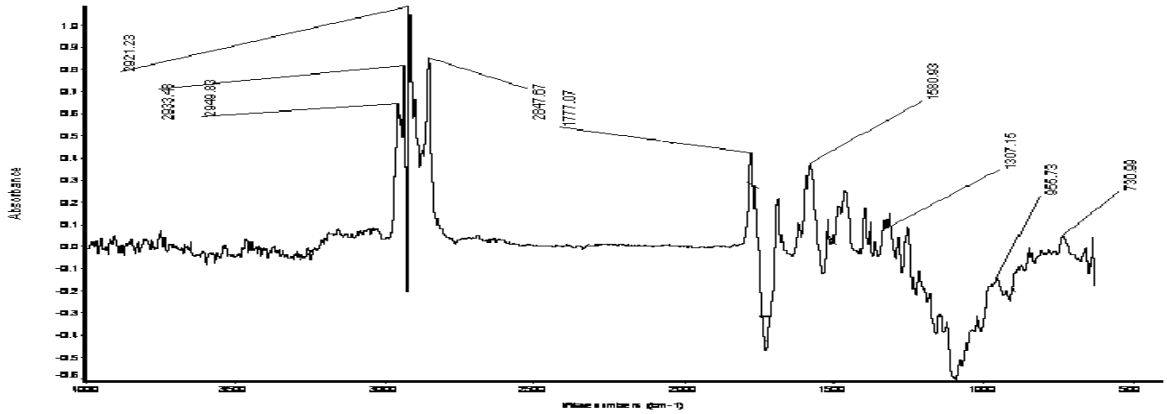


Figure 9. FTIR spectra of amoxicillin with metronidazole

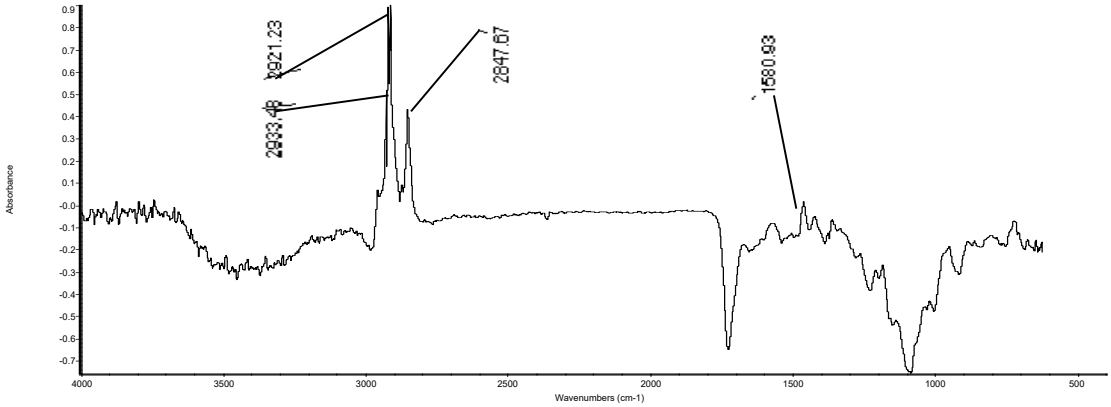


Figure 10. FTIR spectra of metronidazole with amoxicillin

Calibration curve of amoxicillin by HPLC analysis

Concentration (µg/ml)	Peak Area
10	15691
20	36408
30	61243
40	82299
50	100896
60	115097
70	143676
80	162328
90	183077

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100	203827

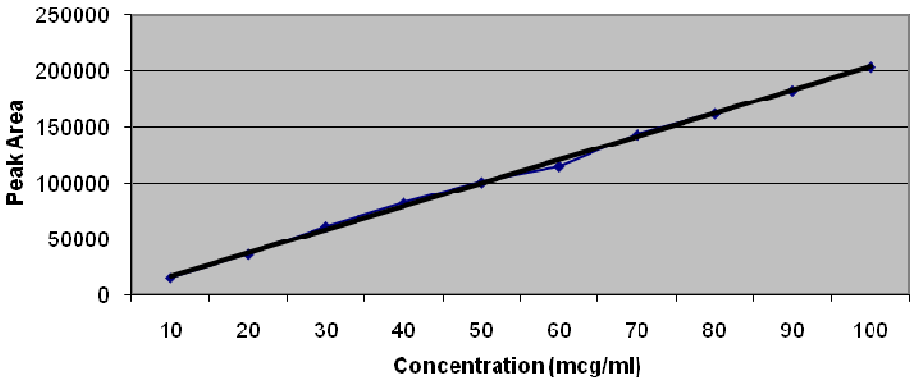

Figure 11. Calibration curve of amoxicillin using HPLC method

Calibration curve of metronidazole by HPLC analysis.

Concentration (µg/ml)	Peak Area
10	72100
20	169154
30	360430
40	429472
50	558466
60	6878395
70	811144
80	934449
90	1057754
100	1181059

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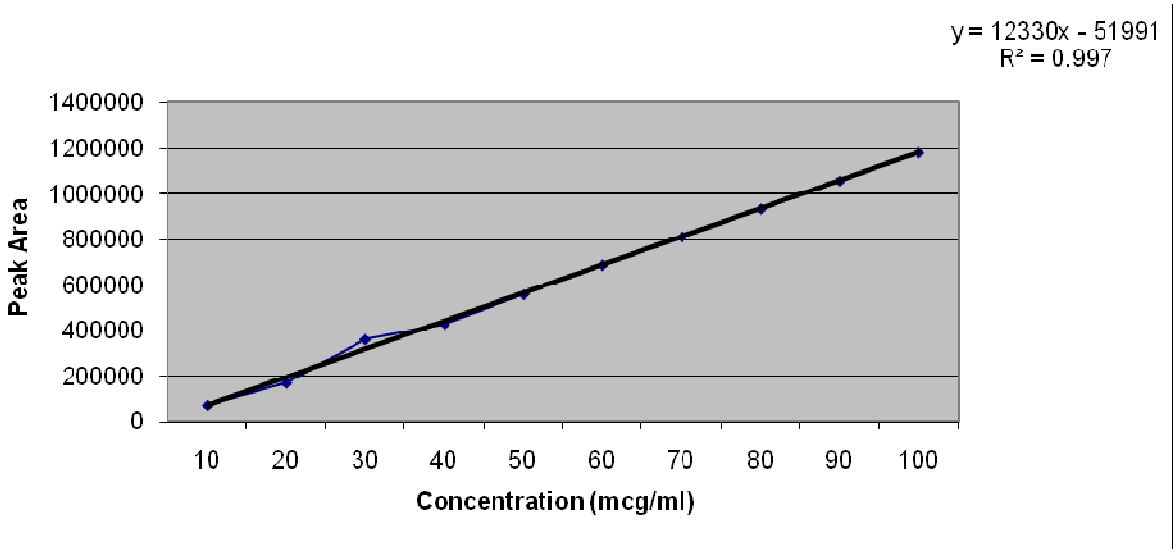

Figure 12. Calibration curve of metronidazole using HPLC method

A chromatograph of both drugs (80µg/ml) is shown in fig. 13, which contains retention time of 2.45 minutes and 7.76minutes for amoxicillin and metronidazole respectively.

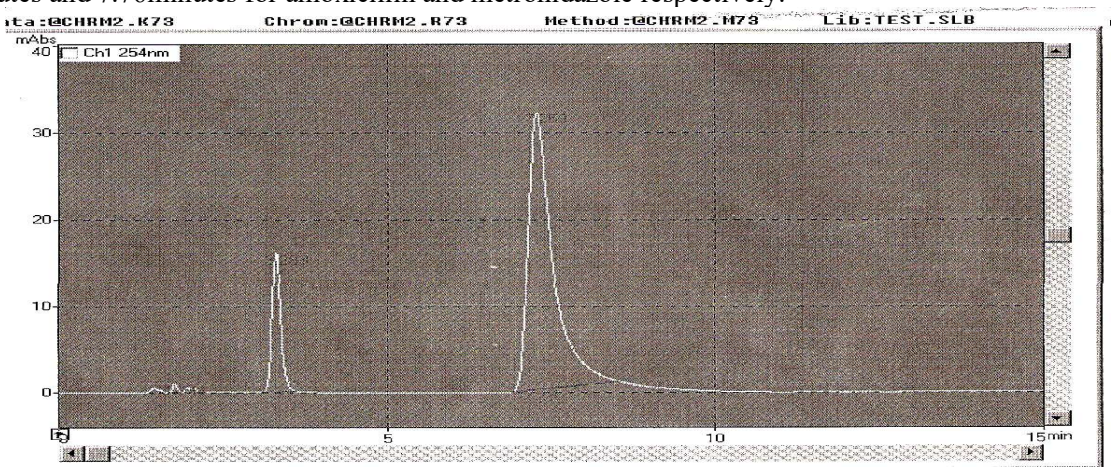

Figure 13. Chromatograph of amoxicillin and metronidazole

Evaluation of floating tablets

General characteristics

Table 3. General characteristics of tablet of all batches

Batch No.	Diameter (mm)	Thickness (mm)	Results
A1	11.05	4.69	Compliance
A2	11.09	4.64	Compliance
A3	11.12	4.54	Compliance

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A4	11.05	4.15	Compliance
A5	11.11	5.45	Compliance
A6	11.06	4.86	Compliance
A7	11.09	4.56	Compliance
A8	11.02	4.49	Compliance
A9	11.01	4.41	Compliance
A10	11.16	4.35	Compliance
A11	11.06	4.33	Compliance
A12	11.09	4.29	Compliance

Some Physical Chemical properties of floating tablet

Table 4. Characterization of tablets of all batches

Batch No.	Weight Variation	Average weight (mg)	Crushing strength (kg/cm^2)	Friability (%)	Drug content (mg/Tablet)	
					Amoxicillin	Metronidazole
A1	0.020±0.15	897.5	4.24±0.35	0.57±0.10	298±0.75	298±0.45
A2	0.028±0.16	891.6	5.00±0.25	0.54±0.13	298±0.45	299±0.79
A3	0.032±0.28	894.3	4.25±0.35	0.75±0.07	298±0.13	298±0.46
A4	0.026±0.14	843.6	5.25±0.35	0.68±0.10	299±0.48	298±0.56
A5	0.030±0.35	1034.4	5.25±0.35	0.45±0.15	298±0.13	299±0.15
A6	0.034±0.48	985.4	4.25±0.35	0.63±0.73	297±0.79	298±0.75
A7	0.036±0.25	967	5.25±0.35	0.73±0.09	298±0.16	299±0.95

A8	0.024±0.35	958.8	4.50±0.35	0.67±0.45	298±0.28	298±0.35
A9	0.026±0.27	947.6	4.25±0.21	0.72±0.49	298±0.82	297±0.15
A10	0.036±0.29	942.6	4.25±0.35	0.61±0.35	298±0.62	298±0.79
A11	0.029±0.26	936.4	4.00±0.46	0.65±0.08	299±0.22	298±0.78
A12	0.031±0.25	923.2	4.25±0.46	0.68±0.45	298±0.68	298±0.75

In Vitro Buoyancy Studies

Three batches (A1 to A3) were prepared using HPMC K 100M, guar hum, and xanthan gum, respectively; sodium bicarbonate was added as a gas generating agent. Sodium bicarbonate induced CO_2 generation in the presence of dissolution media (0.1 N HCL). The gas generated was trapped and protected within the gel formed by hydration of polymer, thus decreasing the density of the tablet. As the density of tablet falls below 1, the tablet becomes buoyant. Batches A2 and A3, containing guar gum and xanthan gum, failed to form a gel with sufficient strength, entrapping CO_2 gas and imparting stable and persistent buoyancy. To study the effect of sodium bicarbonate concentration on floating lag time batches A4 was formulated. The results, shown in Table 4**,** demonstrate that as the amount of sodium bicarbonate decreases, the floating lag time increases. Thus sodium bicarbonate (100mg) was essential to achieve optimum in vitro buoyancy. Although drug release of batch A9 was satisfactory but it could buoyant only for 10 hours that will transit tablet from stomach so batch A8 has been formulated with higher concentration of citric acid that provides 11 hours buoyancy with better release (Photograph 1).

Table 5. Floating lag time and total lag time of all batches

Batch codes	Floating lag time (sec.)	Total floating time (hrs.)
A1	89	7
A2	295	-
A3	No floating	-
A4	160	5
A5	96	13
A6	37	10
A7	29	11
A8	20	11
A9	31	10
A10	42	10
A11	48	10
A12	53	9

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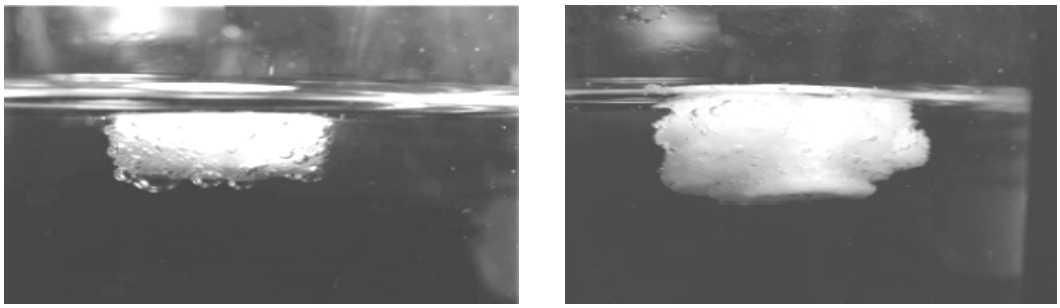

Photograph 1. A. Tablet after floating lag time; B. Tablet before disintegrating

Hydration and Erosion Study

Hydrophilic polymers, in contact with the dissolution medium, may swell and make a continuous gel layer, erode or undergo combination of the two. The swelling action of these polymers is controlled by the rate of their hydration in the dissolution medium. The extent of polymer swelling, relative mobilities of dissolution medium and drug, and matrix erosion dictate the kinetics as well as mechanism of drug release from the polymeric matrices. The objective of the present investigations was to study the rate of hydration and the rate of matrix erosion of different polymers used in various formulation with effect of gas generating agent (sodium bicarbonate), release retarding agent (Stearic acid) and citric acid on polymer swelling and erosion.

Hydration of tablets in 0.1 N HCl (pH 1.2) for 10 hours

Swelling of polymer matrix depends very much on the rate of penetrate entry into the matrix. The results of swelling studies are presented in Table 5. The absorbing water and swelling behavior of HPMC K100M, guar gum and xanthum gum have been describes in Fig. 14. Formulation A2 and A3 was found to be more swelling compared to A1 because HPMC K100M have higher viscosity and low density as compared to other polymer. As same as xanthan gum has more viscosity compare to guar gum so it showed less water absorbity.

Batch Code	Percentage weight gain in hours									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
A1	64.49	102.23	164.7	189.95	250.17	362.99	485.66	666	877.59	1062.3
A2	92.15	125.1	190.93	223.67	280	414.64	555.25	720.92	929.97	1126
A3	89.88	118.03	172.2	190.88	274.68	401.06	535.14	710.8	912.89	1116.19
A4	30.97	57.74	95.74	120.44	186.84	272.55	389.06	500.11	715.66	865.66
A5	84.94	147.35	211.57	248.55	310.67	442.96	562.56	782.24	1006.95	1249.32

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A6	73.56	124.37	195.46	219.16	282.56	401.39	503.94	716.32	996.14	1195.62
A7	72.69	120.45	190.36	215.19	279.43	399.26	501.56	708.75	990	1124.45
A8	72.23	120.56	190.24	212.76	271.06	390.16	499.45	701.51	981.25	1119.12
A9	70.12	118.75	115	207.03	265.34	382.04	496.56	698.15	972.12	1112.45
A10	70.45	119.32	116.63	202.67	264.31	376.64	475.26	692.79	962.35	1096.45
A11	68.36	112.95	113.74	196.92	259.94	371.12	462.32	682.45	959.48	992.53
A12	68.36	112.35	113.83	186.82	250.24	369.45	459.75	675.23	951.42	983.12

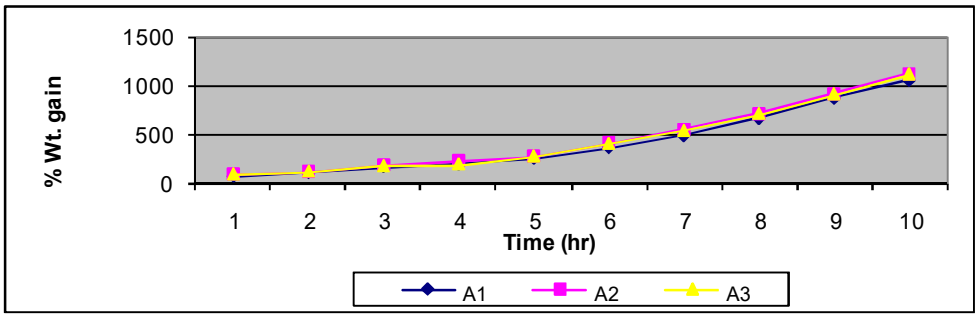

Figure 14. Swelling behavior of formulation A1, A2, and A3-

Fig. 15 shows the effect of gas generating agent (sod. bicarbonate) on swelling. Tablet with higher quantity (100mg) of sodium bicarbonate (A1) was found to be more swelling compare to tablet with less quantity of sodium bicarbonate (A4) due to more capacity of generation of gas. In addition of release retarding agent (A5) swelling was found to be higher than the formulation without stearic acid (A1 to A4) because the maximum uptake of dissolution fluid by stearic acid. Citric acid was not much affect the swelling behavior of tablet due to their lower concentration.

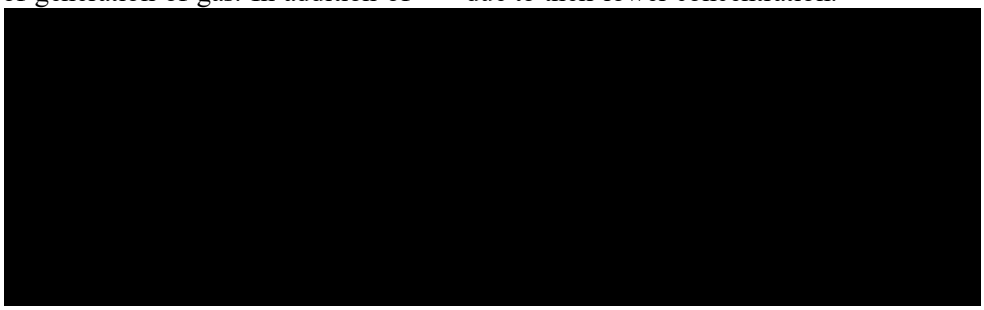

Figure 15. Swelling behavior of formulation A1, A2, and A3

Erosion of tablets in 0.1 N HCl (pH 1.2) for 10 hours

Table 7. Erosion of tablets in 0.1 N HCL (pH 1.2) for 10 hours

Batch Code	Percentage weight loss in hours									
	1	2	3	4	5	6	7	8	9	10
A1	1.19	6.53	14.46	22.47	30.51	42.24	60.16	72.52	84.63	96.11
A2	3.02	9.12	19.96	32.27	37.12	52.45	70.55	80.43	96.32	108.56
A3	2.78	8.88	19.07	31	39.26	55.24	72.3	84.71	99.4	114.52
A4	1.01	4.53	9.64	15.48	21.62	32.74	49.17	60.23	70.14	81.12
A5	1.11	5.49	11.94	17.95	26.45	36.52	56.45	66.62	78.12	90.34
A6	1.08	5.04	14.03	16.82	26	35.25	55.01	64.61	76.75	87.99
A7	1.02	4.92	13.58	15.69	25.55	33.98	53.57	62.6	75.38	85.64
A8	0.96	4.8	13.13	14.56	25.1	32.71	52.13	60.59	74.01	83.29
A9	0.9	4.68	12.68	13.43	24.65	31.44	50.69	58.58	72.64	80.94
A10	0.84	4.56	12.23	12.3	24.2	30.17	49.25	56.57	71.27	78.59
A11	0.78	4.44	11.78	11.17	23.75	28.9	47.81	54.56	69.9	76.24
A12	0.72	4.32	11.33	10.04	23.3	27.63	46.37	52.55	68.53	73.89

In hydrophilic polymeric matrix systems, the carrier on the surface of the matrix initially hydrates during dissolution to generate an outer viscous gel layer and then sequentially followed by matrix bulk hydration, swelling and erosion. The results of erosion studies are presented in fig. 16. Formulation A1 was found to be lower erosion compared to A2 and A3 because HPMC K100M have higher viscosity as compared to guar gum and xanthan gum. Fig 17 shows the effect of gas

generating agent (sod. bicarbonate) on erosion, erosion of polymer was found to be more of batch A1 than the batch A4 due to less amount of gas generating agent. In addition of release retarding agent, stearic acid, erosion of polymer from batch A5 was found to be lower than the batch A1 because of raised viscosity. Citric acid concentration was not much affect the erosion of polymer due to their lower concentration.

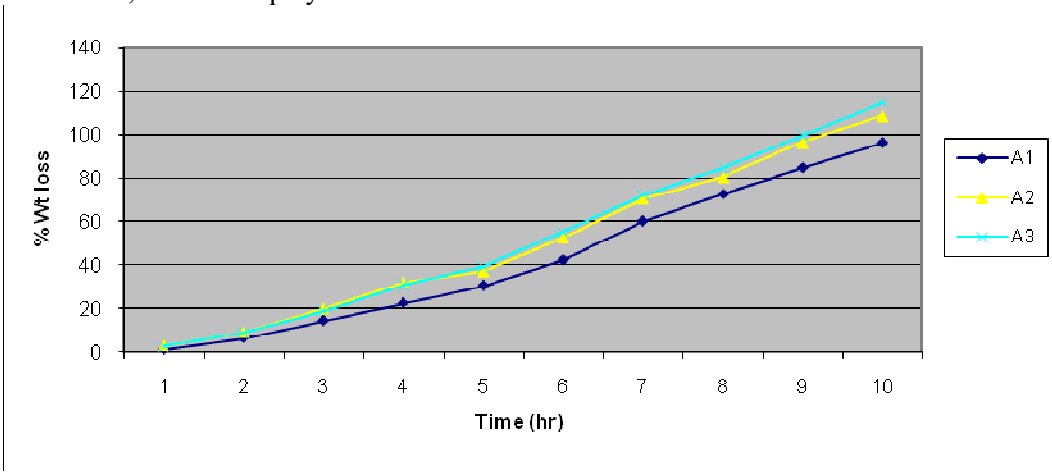

Figure 16. Erosion of batch A1, A2 an A3

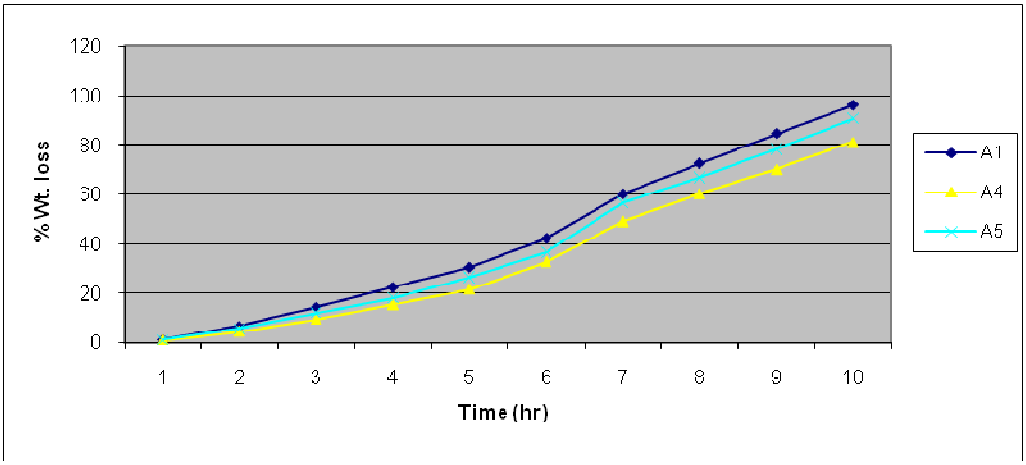

Figure 17. Erosion of batch A1, A4 an A5

Effect of different polymers on in vitro drug release

Batch A1, A2 and A3 consist HPMC K100M, Guar gum and xanthan gum respectively. Results revel that drug release was based on the viscosity of polymers as HPMC K100M showed slowest release among all three polymers because of higher viscosity and lower swelling rate, then this results was followed by xanthan gum and guar gum. A comparative in vitro amoxicillin release has been shown in fig 18.

Effect of gas generating agent on in vitro release.

As the concentration of sodium bicarbonate decreased from 100 mg to 50 mg (A1 to A4), release of amoxicillin decreases. As it has shown in fig 19, that A1 releases total amoxicillin in 8 hours while A4 acquires 9 hours to release it. On the other hand, all batches release metronidazole faster than amoxicillin. This might me due to the alkaline nature of sodium bicarbonate. Sodium bicarbonate creates an alkaline environment and metronidazole is more soluble in alkaline nature. It can be observed in Fig 20.

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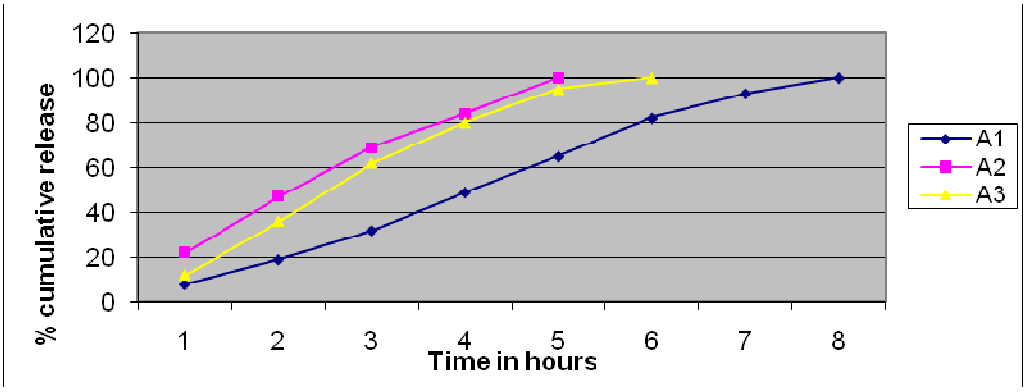

Figure 18. *In Vitro* release of Batch A1, A2, and A3

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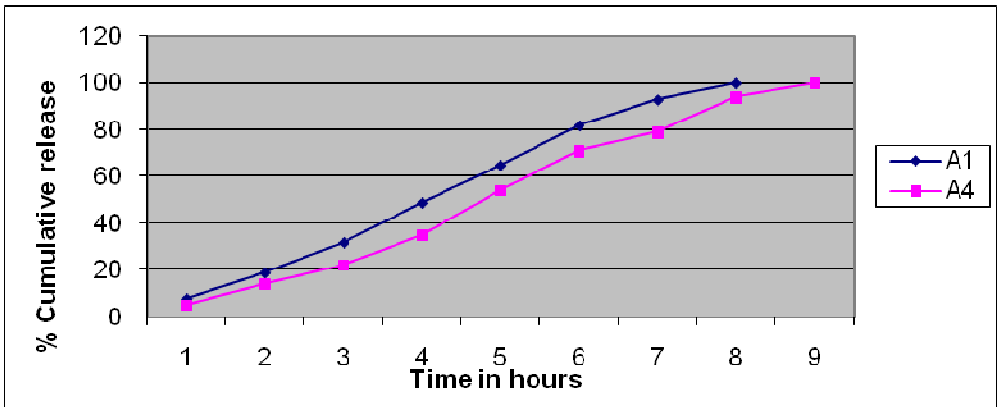

Figure 19. *In Vitro* release of Batch A1and A4

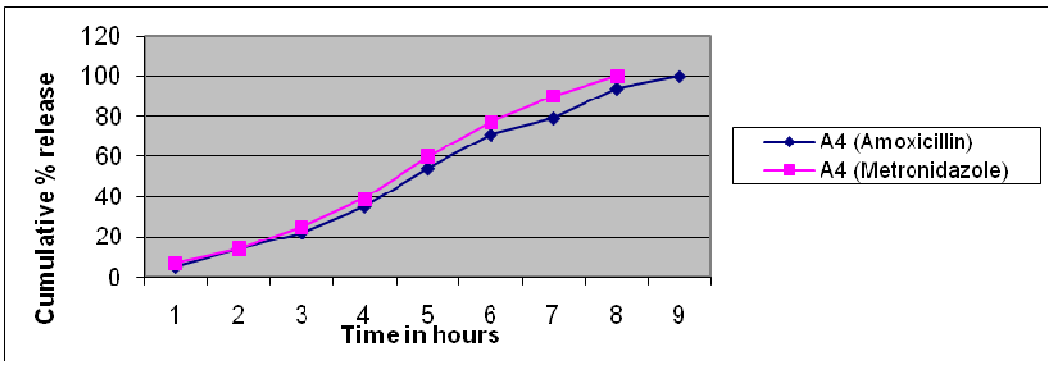

Figure 20. *In Vitro* release of Amoxicillin and Metronidazole from batch A4

Effect of stearic acid on in vitro release

In order to reduce drug release profile from the formulation, stearic acid was added in to the formulation. As the concentration of stearic acid increases from 0 to 100 mg/tablet, initial burst releases as well as drug release in the later hours have been increased as shown in fig. 21. In case of formulation containing 0 mg (A4) and 50 mg (A6) stearic acid, cumulative drug (amoxicillin) release after 8 hours was 88 and 100% respectively. The formulation containing 100 mg (A5) stearic acid released 100% amoxicillin in 13 hours.

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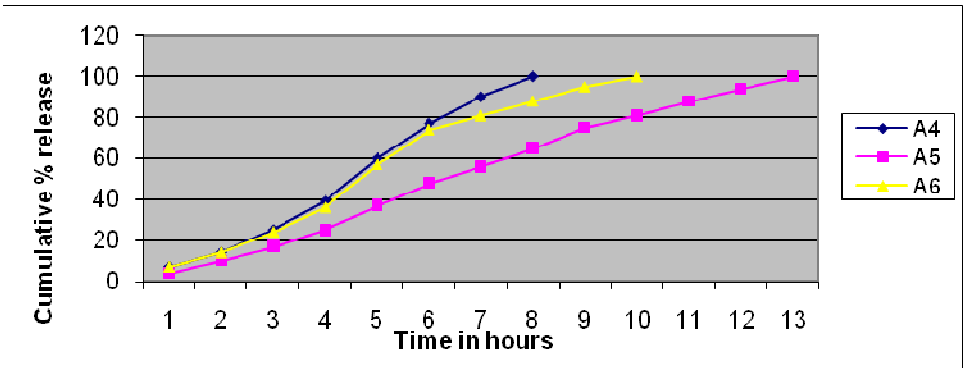
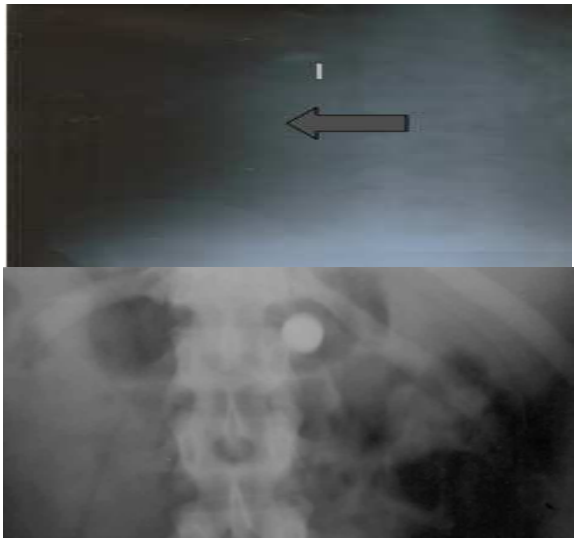


Figure 21. *In Vitro* release of Batch A4, A5, and A6

***In vivo* buoyancy studies**

The behavior of the tablet in the stomach was observed in real time using a radiographic imaging technique. On radiographic images made 0.5 h after the administration, the tablet was observed in the stomach of human volunteer (Photograph 2A). Next picture taken at 1 h significant changes were detected the tablet has changed its position and turned round (Photograph 2B). This provided evidences that tablet was not adhering to gastric mucus, on the contrary floated on gastric fluid. Additionally after 150 minutes the swelling of the tablet is visualized very well together with the white dry core and translucent swelling layer around it (Photograph 2B).

As the swelling continued the glassy core diminished, the swelling layer eroded from the outer surface and a size reduction was seen. Results have shown that gastric residence time was 420 minutes than tablet disintegrated and catheterized particles in small intestine.



Photograph 2. Intragastric behavior of prepared $Baso_4$ loaded floating tablet
2A. Tablet after 0.5 h of the administration; 2B. Tablet 1.5 h of the administration.

Conclusion

Helicobacter Pylori is a gram-negative rod that colonized the mucus on the luminal surface of the gastric epithelium and identified as a causative factor in etiology of peptic ulcer disease. No single antibiotic has been able to eradicate this organism effectively, due to development of resistance, therefore multiple drugs therapy is needed. So two antibiotics, metronidazole and amoxicillin, were selected for present research work. Conventional dosage forms of both drugs have certain limitations, which could be overcome

by preparing a combinational floating tablet of both drugs and it would put some other advantages as well.

First of all a noneffervescent floating drug delivery was used to achieve in vitro buoyancy. In the initial batches tablets prepared using polymers such as HPMC K100M, guar gum and xanthan gum did not exhibit sufficient swelling o provide in vitro buoyancy. An effervescent approach was then adopted. Three batches (A1 to A3) were prepared using HPMC K 100M, guar hum, and xanthan gum, respectively; sodium bicarbonate was added as a gas generating agent. Sodium bicarbonate induced CO_2 generation in the presence of dissolution media. The gas generated was trapped and protected within the gel formed by hydration of polymer, thus decreasing the density of the tablet. As the density of tablet falls below 1, the tablet becomes buoyant. Batches A2 and A3, containing guar gum and xanthan gum, failed to form a gel with sufficient strength, entrapping CO_2 gas and imparting stable and persistent bouncy. To study the effect of sodium bicarbonate concentration on floating lag time batches A4 was formulated. The results demonstrate that as the amount of sodium bicarbonate decreases, the floating lag time increases and total floating time decreases. Thus sodium bicarbonate (100mg) was essential to achieve optimum in vitro buoyancy.

Fed condition and presence of *H. Pylori* elevate pH of stomach so citric acid was incorporated in formulation to provide an acidic medium for sodium bicarbonate. However, adding citric acid to formulation might enhance dissolution, stearic acid was incorporated in the formulations to sustain release. Decreasing concentration of stearic acid in formulations (A9 to A12), raised drug release profile and decreased total floating time of tablets. Only one batch, A9, showed sufficient drug release (11 hours) but it could float only for the 10 hours.

Finally batch A8 formulated with higher quantity of citric acid compared to A9, which improved total floating time of tablet, from 10 to 11 hours. Both batches (A8, A9) released drugs in almost same time (11 hours) but floating time was improved in batch A8 compare to A9 due to raised quantity of citric acid.

Tablets of batch A8 compliance all pharmacopeial standards like hardness, friability, weight variation and drug content. In vitro release of both drugs was 11 hours with improved floating time. Results of *in vivo* bouncy study of tablet (A8) was also satisfactory, it reveals that tablet floated for 420 minutes in stomach. So it can be concluded that Batch A8 have all characteristics, which a floating tablet should have and it is best in all twelve formulations.

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