ejpmr, 2019,6(11), 506-518

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION, EVALUATION AND CHARACTERIZATION OF FLOATING TABLET OF AZITHROMYCIN FOR HELICOBACTOR PYLORI

Neha Arora[1], Yogesh Matta[1], Dr. Sonu Sharma[1], Saurabh Sharma[1], Sandeep Singh[1], Md Dabeer Ahmad[2]

[1]School of Pharmaceutical Sciences, Jaipur National University, Jagatpura, Jaipur.
[2]Department of Pharmaceutical Sciences, College of Pharmacy, Aldowadmi, Shaqra University KSA.

***Corresponding Author: Mr. Yogesh Matta**

Assistant Professor, School of Pharmaceutical Sciences, Jaipur National University, Jagatpura, Jaipur.

Article Received on 23/09/2019 **Article Revised on 13/10/2019** **Article Accepted on 02/11/2019**

ABSTRACTS

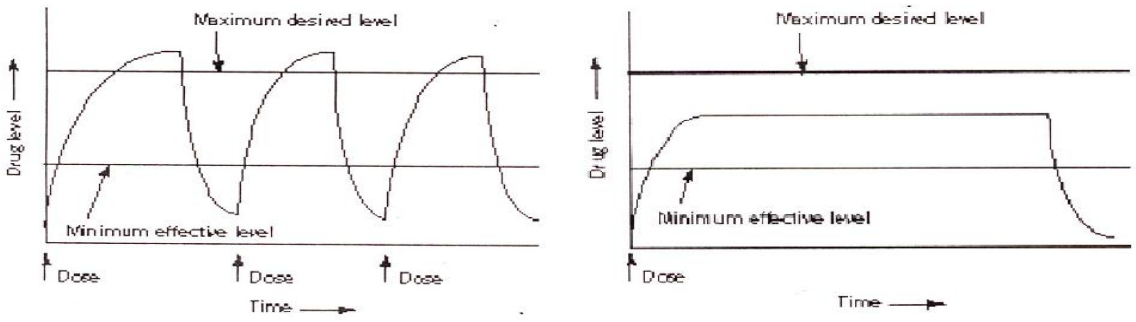
Oral route has been the most popular and successful route used for controlled delivery of drugs. Controlled release of drug delivery system (CRDDS) optimizes the biopharmaceutical, pharmacokinetic, pharmacodynamic, properties of drugs and to reduce the side effects and to designed to deliver the drug in such a way that the levels are maintained within the therapeutic window effective for a long period till the system continuous to deliver the drug at a particular rate. In present study, an attempt was made to formulate floating tablet of Azithromycin in order to enhance bioavailability, reduce dose thereby improve patient compliance. Preformulation studies were done to characterize the chemical and physical properties of drug. FT-IR spectrum and melting point determination confirmed identity and purity of Azithromycin. Azithromycin was subjected to compatibility studies with different excipients, there was no physical change observed in drug and excipients. Further, it was confirmed by taking FT-IR graphs.

KEYWORDS: Azithromycin, Excipients, Pharmacokinetic, Pharmacodynamic, Bioavailability.

INTRODUCTION

Oral Drug Delivery Systems

Oral route has been the most popular and successfully used for controlled delivery of drugs because of convenience and ease of administration. The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in controlling the release rate of drug. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. Drugs that are easily absorbed from the gastrointestinal tract and have a short half-life are eliminated quickly from the blood circulation. To reduce this problem, the oral controlled release (CR) formulations have been developed, as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period of time. This minimizes several potential problems like saw-tooth kinetics characterized by large peaks and troughs in the drug concentration time curve.



A **B**

Fig. 1: Plasma level profiles followings (A) Conventional and (B) Controlled release dosing.

Gastroretentive Drug Delivery Systems

It has been suggested that formulating the drugs with narrow absorption window in a unique pharmaceutical dosage form with gastroretentive properties, would enable an extended absorption phase of these drugs. After oral administration, such a dosage form would be retained in the

stomach and release the drug there in a extended manner, so that drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. Gastroretentive dosage form releases medications in a controlled manner which extends the absorption phase of drugs characterized by a limited and narrow absorption window at upper part of gastrointestinal tract or drugs intended to treat local ailments in gastroduodenum. The need for gastroretentive dosage forms has led to extensive efforts in both academia and industry towards the development of such drug delivery systems.

Gastroretentive technologies

Various techniques have been pursued to increase the GRT of dosage forms by employing a variety of concepts such as floating, swelling, inflation and adhesion. These systems have been classified according to the basic principles of gastric retention.

- Floating drug delivery system (FDDS), with low density providing sufficient buoyancy to float over the gastric contents.
- High density, which retain the dosage form in the body of stomach for longer period of time, by sedimenting to the folds of stomach.
- Bioadhesion to gastric mucosa, enabling the localized retention of the system in the stomach.
- Expansion by swelling or unfolding to a large size which limits emptying of the dosage form through pyloric sphincter.

Helicobacter pylori

A peptic ulcer is a sore on the lining of the stomach or duodenum, the beginning of the small intestine. Less commonly, a peptic ulcer may develop just above the stomach in the oseophagus, the tube that connects the mouth to the stomach. A peptic ulcer in the stomach is called a gastric ulcer. One that occurs in the duodenum is called a duodenal ulcer.

People can have both gastric and duodenal ulcers at the same time. They also can develop peptic ulcers more than once in their lifetime. Peptic ulcers are common. Each year in the United States, about half a million people develop a peptic ulcer.

Causative agents for peptic ulcers

A bacterium called Helicobacter pylori (H.pylori) is a major cause of peptic ulcers. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as asprin and ibuprofen, are another common cause.

Rarely, cancerous or noncancerous tumors in the stomach, duodenum, or pancreas cause ulcers. Peptic ulcers are not caused by stress or eating food, but both can make ulcer symptoms worse. Smoking and drinking alcohol also can worsen ulcers and prevent healing.

Life Cycle of H.Pylori

H.pylori is a gram negative spiral shaped bacteria. In humans, it colonises the stomach and the likelihood of infection increases with age. In the U.K, half of those over 50 are infected. There is some evidence that H.pylori may be associated with gastric cancer. There is no convincing evidence, at present, for a relation between H.pylori and non ulcer dyspepsia.

H.pylori infection by itself is not sufficient to cause peptic ulcers, other factors are needed. These may include hypersecretion of acid, smoking and genetic predisposition.

Helicobacter pylori is an important cause of peptic ulcer disease and chronic gastrititis and has been linked to the pathogensis of gastric malignancy. The bacterium causes peptic ulcers by damaging the mucous coating that protects the stomach and duodenum. Damage to the mucous coating allows powerful stomach acid to get through to the sensitive lining beneath. Together, the stomach acid and H.pylori irritate the lining of the stomach or duodenum and causes ulcer. For these reasons, anti-H.pylori regimens are being investigated with increasing frequency, with about 1500 reports being published between 1984 and 1999. Many combinations of antibiotics and antisecretory drugs have been tested in an attempt to find the optimal regimen. The regimen of choice should be cheap, simple, of short duration, associated with few side-effects, and with an efficacy of 90% or greater. The most popular strategies for producing a high rate (80-95%) of H.pylori eradication entail the use of two antibiotics given for atleast 1week. The use of antibiotics for shorter periods has been investigated infrequently, as a increased daily dose considered necessary is thought to be associated with an increase in side-effects.

Azithromycin is a potentially attractive therapeutic agent for H.pylori, given its excellent mean inhibitory concentration for this organism and long biological half life.

MATERIALS METHODS

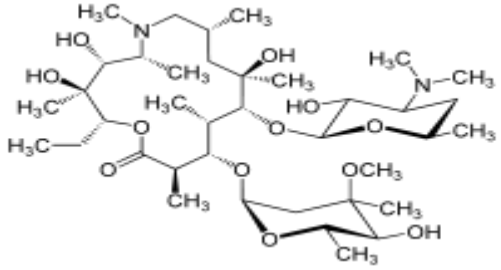
Drug Profile

Common name: Azithromycin

Chemical name: (2R,3R,4R,5R,8R,10,11R,12S,13S,14R,)-11-{[(2S.3R,4S,6R)-4-(dimethylamino)- 3hydroxy-6-methyloxan-2-yl]oxy} -2-ethyl-3,4,10-trihydroxy-13-{[(2R,4R,5S,6S)-5-hydroxy- 4-methoxy-4,6-dimethyloxan-2-yl]oxy}-3,5,6,8,10,12,14-heptamethyl-1-oxa-6azacyclopentadecan-15one.

Molecular formula: $C_{38}H_{72}N_2O_{12}$

Structural formula



Molecular Weight: 748
Description: It is white or almost white crystalline powder.
Solubility: Practically insoluble in water, freely soluble in ethanol and in methylene chloride.
Therapeutic category: Antibiotic
Melting point: 113-115°C
Odour: Odourless

Mechanism of action: Azithromycin prevents bacteria from growing by interfering with their protein synthesis It binds to the 50S subunit of the bacterial ribosome, and thus inhibits translation of mRNA. Nucleic acid synthesis is not affected.

Uses: Azithromycin is used to treat many different infections, including acute otitis media, nonstreptococcal bacterial pharyngitis, gastrointestinal infections such as traveler's diarrhea, respiratory tract infections such as pneumonia, cellulitis.

Pharmacokinetics: Azithromycin is acid-stable, so it can be taken orally with no need of protection from gastric acids. It is readily absorbed, but its absorption is greater on an empty stomach. Time to peak concentration in adults is 2.1 to 3.2 hours for oral dosage forms and one to two hours after a dose. Due to its high concentration in phagocytes, azithromycin is actively transported to the site of infection. During active phagocytosis, large concentrations are released. The concentration of azithromycin in the tissues can be over 50 times higher than in plasma, due to ion trapping and its high lipid solubility(volume of distribution is too high).

Metabolism: According to Davis Drug Guide for Nurses, following a single 500 mg dose, the half-life of azithromycin is 11–14 h. The longer half-life of 68 h is achieved only when multiple doses are consumed. Biliary excretion of azithromycin, predominantly unchanged, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Side effects: Most common side effects are gastrointestinal: diarrhea (5%), nausea (3%), abdominal pain (3%), and vomiting. Fewer than 1% of patients stop taking the drug due to side effects. Nervousness, dermatologic reactions, and anaphylaxis have been reported. As with all antimicrobial agents, pseudomembranous colitis can occur during and up to several weeks after azithromycin therapy.

METHODOLOGY

Characterization of drug

The procured sample of azithromycin was characterized in terms of its physical description, organoleptic properties, melting point and solubility in various solvents.

Establishment of calibration plot

To conduct the drug dissolution studies, standard plots for pure drug were constructed by using method described by Preeti Gandhi *et al*. The absorbance of prepared solutions of azithromycin in 0.1N HCl was measured at 254nm in Shimadzu UV-1700 spectrophotometer against an appropriate blank (0.1N HCl).

Preliminary studies

During preliminary studies various polymers *viz.* HPMC K4M, HPMC K100 and, Carbopol 934, were tried for formulating oral sustained release floating tablets of azithromycin. Tablets were prepared using each of these polymers and using various polymers in different ratio to formulate floating azithromycin tablets.

Preparation of granules

Azithromycin was mixed with various grades of HPMC in varying ratio. These batches are mostly prepared by wet granulation method.

Evaluation of granules

Angle of repose

Flow properties of the granules are evaluated by determining the angle of repose. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plane. It is a qualitative assessment of the internal cohesive and frictional effects under low levels of external loading as might apply in powder mixing, on in tablet die or capsule shell filling operation.
$\tan \theta = h/r$

Bulk density

The ratio of mass to volume is known as density of material. The bulk density is determined by pouring the weighed sample in to a graduated cylinder via a large funnel and measuring its volume.

Tapped density is determined by placing a graduated cylinder containing a non mass of formulation on a mechanical tapper apparatus which is operated at a fix no. of taps until the powder volume has reached a minimum. LBD and TBD were calculated using the following formula.
LBD = weight of the powder / volume of the packing
TBD = weight of the powder / tapped volume of the packing

Compressibility index
Compressibility index is a simple indication of the ease with a material can be induced to flow. The compressibility index and Hausner index are the measure of porosity of a powder to be compressed. They measure the relative importance of interparticulate interaction. For poorer flowing materials, there are frequently greater interparticulate interactions and greater difference between the bulk and tapped densities. These differences are reflected in the compressibility index and Hausner index.

Compressibility index of the powder was determined by Carr's compressibility index as given by following eqn.
Carr's index (%) = [(TBD – LBD) x 100]/TBD

Hausner ratio
Hausner ratio of the powder was determined by Hausner index as given by the following equation:
Hausner index = TBD/LBD

Compression of granules
The dried granules were first mixed with magnesium stearate and talc. The granules were then compressed into tablets of average weight 700 mg containing 250mg of azithromycin On a 16 station rotary tablet machine in biconvex shape**.**

Evaluation of floating tablets
The prepared tablets were evaluated for quality control tests like hardness, thickness, friability and drug content uniformity, weight variation, thickness, *in vitro* dissolution studies and analysis of dissolution data, *in vitro* buoyancy test and swelling index determination.

Tablet hardness
The mechanical strength of tablets is an important property. It has been described by various terms including fracture resistance, hardness, bending strength and crushing strength. Tablet hardness has been defined as the force required breaking a tablet in a diametric compression test.

Friability
Friability test was done by Roche friabilator. Six tablets were weighed and were subjected to combined effect of attrition and shock by utilizing a plastic chamber that resolve at 25 rpm dropping the tablets at distance of 6 inch with each revolution. Operated for 100 revolutions, the tablets were dusted and reweighed. The percentage friability was calculated. The average hardness and standard deviation was determined.
Percent friability = $[(Weight_{final} – Weight_{original}) / Weight_{original}] \times 100$

Uniformity of weight
Twenty tablets from each batch were individually weighed and their average weight was calculated. From the average weight of the prepared tablets, the standard deviation was determined.

Drug content uniformity
To evaluate a tablet's potential for efficacy; the amount of drug per tablet needs to be monitored from tablet to tablet and batch to batch.

Thickness
The dimensions of the tablet like thickness, length were measured using vernier-calipers. Ten tablets from each batch were selected randomly for this test and the average value was reported.

***In vitro* buoyancy test**
The *in vitro* buoyancy was determined by floating lag time, per the method described by Rosa et al. The tablets were placed in a 100 mL beaker containing as 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time (FLT) and the time period up to which the tablet remained buoyant is determined as Total Floating Time (TFT).

Swelling index determination
The swelling behavior of dosage unit can be measured either by studying its dimensional changes, weight gain, or water uptake. Water uptake study of the dosage form is conducted by using dissolution apparatus-II in 900 mL of distilled water which is maintained at 37±0.5°C, rotated at 50 rpm. At selected regular intervals, the tablet is withdrawn and weighed. Swelling of the tablet is expressed as Swelling index (SI). The swelling index of optimized formulation was calculated using the formula shown in equation.
$SI= (W_2 - W_1) / W_1$

Fourier transform infra-red (FTIR) studies
The FTIR spectra of the drug and its physical mixtures with polymer blend of selected best formulation were recorded in KBR using an FTIR spectrophotometer.

RESULTS AND DISCUSSION

Preformulation Studies
Characterization of drug
A). Physical Description
Azithromycin was found to be white crystalline powder with no odour and taste.

Table no 1: Physical properties of Azithromycin.

Sl. No	Physical property	Interpretation
1	Nature	Crystalline powder
2	Colour	White
3	Odour	Odourless
4	Taste	Tasteless

B). Melting Point

Table no 2: Melting point of Azithromycin.

The Melting point of Azithromycin was found to be 113^0C by Capillary fusion method.

Method employed	Experimental value	Literature value
Capillary fusion method	113-115^{0}C	113^{0}C

C). Solublity: The solubility of Azithromycin was determined in different solvent systems. An excess quantity of the drug was mixed with 10ml of each solvent in screw capped glass tubes. The solutions were examined physically for the absence or presence of drug particles for qualitative determination of drug Azithromycin was soluble in water and dilute solution of hydrochloric acid. It freely soluble in Dilute Hydrochloric acid and insoluble in water.

D). Determination of λ_{max}: The absorption maximum of drug Azithromycin was found by using double beam UV spectrophotometer and it was 254nm.

E). Preparation of Calibration plot: Absorbance data for standard calibration curves are given in table 1. Using the absorbance of azithromycin at varied concentration, calibration curve was constructed. The calibration equation for straight line was observed to be Y=0.034x+0.005 with correlation coefficient as 0.999, this was further used for determination of concentration of unknown samples.

Table 3: Calibration data for calibration plot of azithromycin in 0.1N HCl (λ_{max}=254nm).

Sl. No.	Concentration(µg/ml)	Absorbance(mean±SD)
1.	Blank	0.000±0.00
2.	2	0.071±0.08
3.	4	0.146±0.09
4.	6	0.210±0.07
5.	8	0.285±0.08
6.	10	0.351±0.07
7.	12	0.422±0.06
8.	14	0.494±0.01
9.	16	0.562±0.06
10.	18	0.620±0.09
11.	20	0.684±0.13

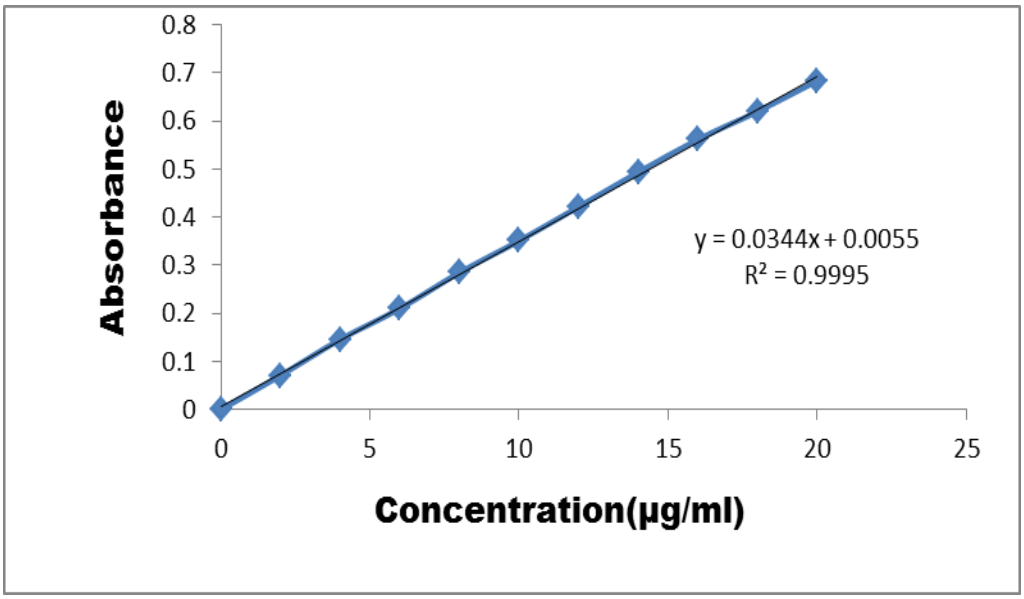


Fig 2: Standard Calibration Curve of Azithromycin in 0.1N HCl(λ_{max}=254nm).

F). Compatiblity studies of drug and polymer

The FTIR Spectra of Azithromycin is shown in fig.

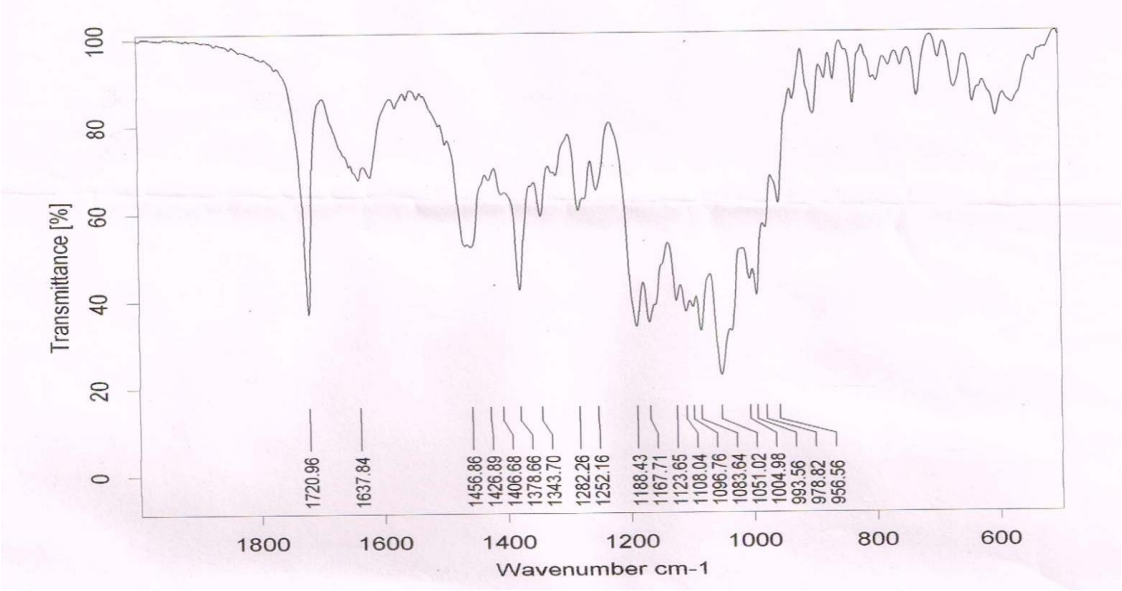


Fig no. 3: FTIR Spectra of Azithromycin drug.

2 Preliminary Studies

During preliminary studies various polymers *viz.* HPMC K4M, HPMC K100M, Carbopol 934, were tried for formulating oral sustained release floating tablets of azithromycin. Tablets were prepared using each of these polymers and using various polymers in different ratio. Subsequently depending upon the results obtained shown in table 8.

Table 4: Preliminary trial formulations.

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6
Drug	500	500	500	500	500	250
HPMC K4M	80	-	-	50	50	200
HPMC K100M	-	80	-	100	100	-
Carbopol 934	-	-	80	-	60	-
Sod.bicarbonate	70	70	70	70	70	70
DCP	32	32	32	62	-	162
Mg.stearate	10	10	10	10	10	10

Table 5: Formulations development batches.

Ingredient	S1	S2	S3	S4	S5	S6
Azithromycin	250	250	250	250	250	250
HPMC K4M	150	200	125	100	100	140
HPMC K100M	50	-	-	100	70	60
Carbopol 934	-	-	75	-	30	-
DCP	145	145	145	145	145	145
Sod. bicarbonate	75	75	75	75	75	75
Mag.stearate	20	20	20	20	20	20
Talc	8	8	8	8	8	8
Aerosil	2	2	2	2	2	2

Evaluation of granules

The prepared granules were evaluated by evaluating their Angle of Repose, Bulk density/Tapped density, Compressiblity index, Hausner ratio. The results for Formulation development batches are shown in table no. 10.

Table no. 6: Resuls of precompression flow properties of granules of Azithromycin of Formulation development batches.

Formulation code	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio(H_R)
S1	30.12	0.2802	0.3356	16.50	1.19
S2	26.96	0.3162	0.3562	11.22	1.12
S3	31.27	0.2706	0.3046	11.16	1.12
S4	29.52	0.3262	0.3674	11.21	1.12
S5	28.30	0.3257	0.3821	14.76	1.17
S6	29.80	0.3002	0.3675	18.31	1.22

(n=3)

Preparation of floating matrix tablets of Azithromycin

The granules were compressed into tablets using 16 station rotary tablet machine in biconvex shape.

Evaluation of floating matrix tablets of Azithromycin

A). Physical Parameters

The prepared tablets were evaluated for quality control tests like hardness, friability and drug content uniformity, weight variation. The results are shown in table. No.11.

Table 7: Result of physical parameters and drug content for all tablet formulations of azithromycin.

	Hardness(kg/cm^2) Mean ±SD (n=5± SD)	Friability (%)	Weight variation Mean ±SD (n=3±SD)	Drug content (%)	Length(mm) Mean ±SD	Thickness (mm) Mean ±SD
S1	6.5±0.4	0.57	676.1±3.2	106.3±1.7	17.01±0.5	5.2±.002
S2	7.5±0.2	0.46	701.8±7.9	108.4±2.1	17.01±0.5	5.2±.005
S3	6.5±0.1	0.66	678.1±12.8	104.5±2.2	17.01±0.5	5.1±.003
S4	6.5±0.2	0.51	700.0±5.2	104.6±1.7	17.01±0.5	5.7±.005
S5	7.0±0.3	0.43	706.6±6.1	105.5±1.2	17.01±0.5	5.6±.004
S6	7.5±0.2	0.37	696.0±6.0	105.4±1.6	17.01±0.5	5.8±.002

(n=3)

B). Invitro studies

I). Buoyancy test

The results of in vitro buoyancy study and of formulation development batches are shown in table no. 12 and in Fig(1-7).

Table 8: Results of *in vitro* buoyancy study of formulation development batches of azithromycin floating tablets.

Formulation code	Floating lag time (sec) (n=3±SD)	Floating time(hrs)
S1	**129±11**	**>12**
S2	**75±12**	**>12**
S3	**145±6**	**>8**
S4	**124±10**	**>12**
S5	**185±12**	**>10**
S6	**170±6**	**>12**

(n=3)

The floating time for further optimized batches (S1-S6) was found to be in the ranged of (>8 to 12hrs). For the final optimized formulation (S2) floating lag time and floating time were found to e 75±12sec and 12hrs, respectively.

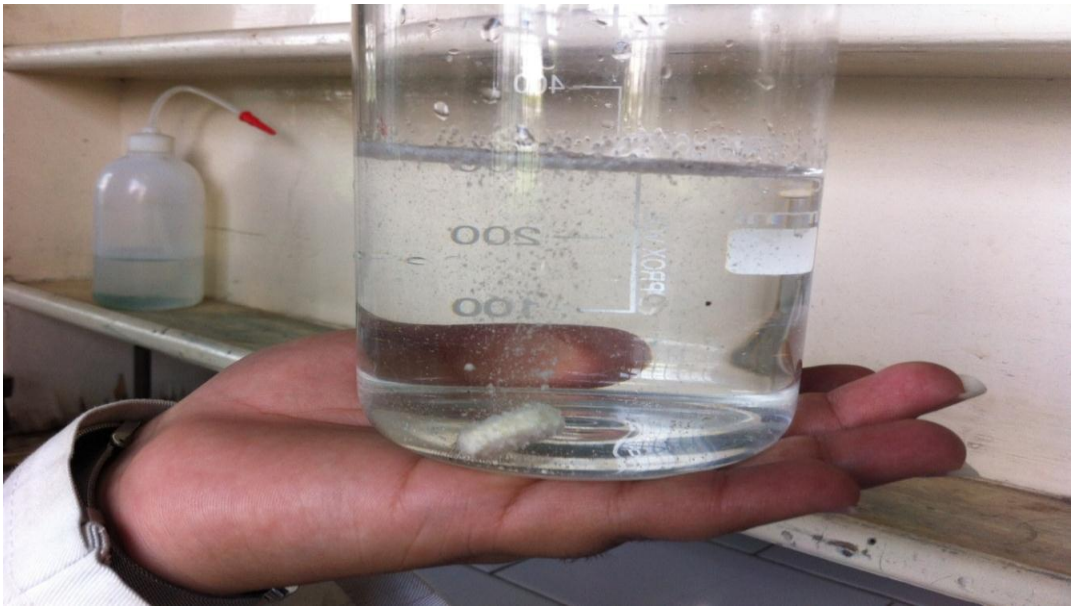


Fig no 4: Floating properties of Azithromycin tablet S2 at 44 sec.

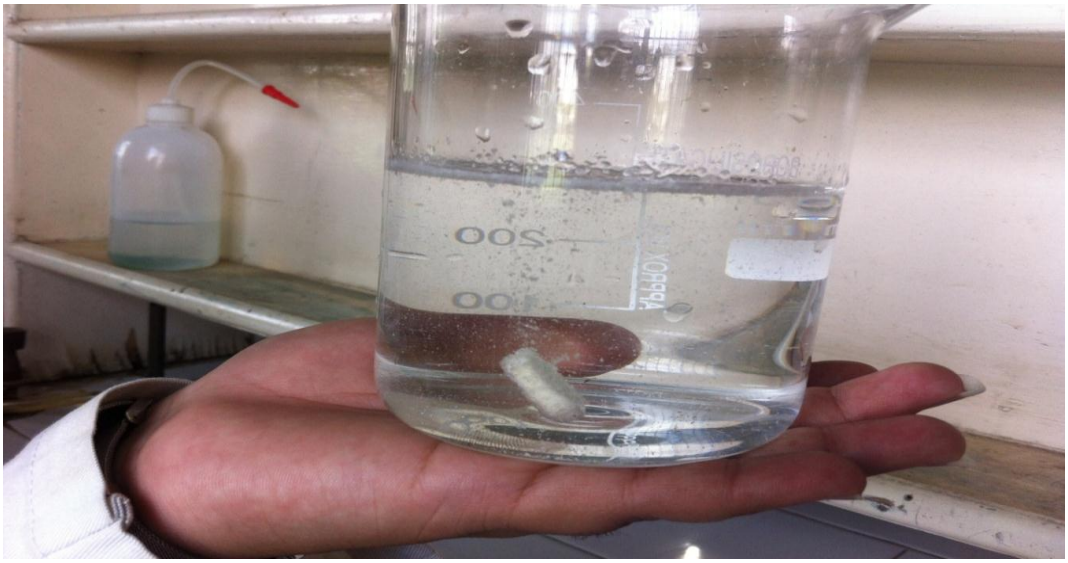


Fig no 5: Floating properties of Azithromycin tablet of S2 at47 sec.

Fig no 6: Floating properties of Azithromycin tablet S2 at 53 sec.

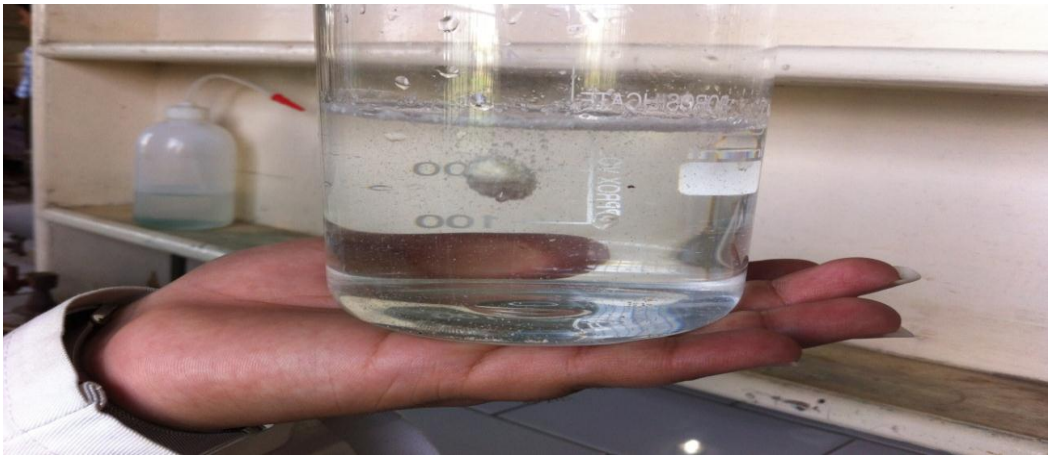


Fig no 7: Floating properties of Azithromycin tablet S2 at 62 sec.

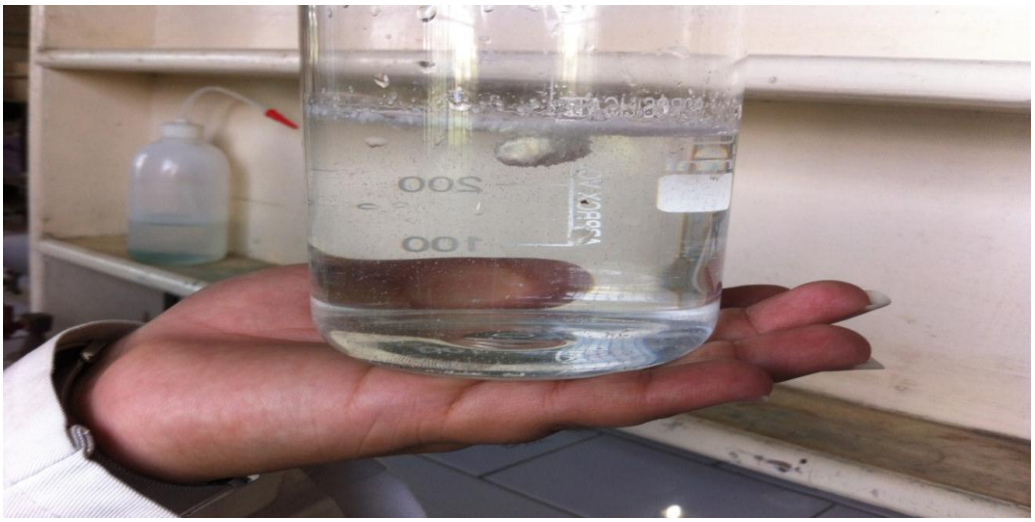


Fig no 8: Floating properties of Azithromycin tablet S2 at 66 sec.

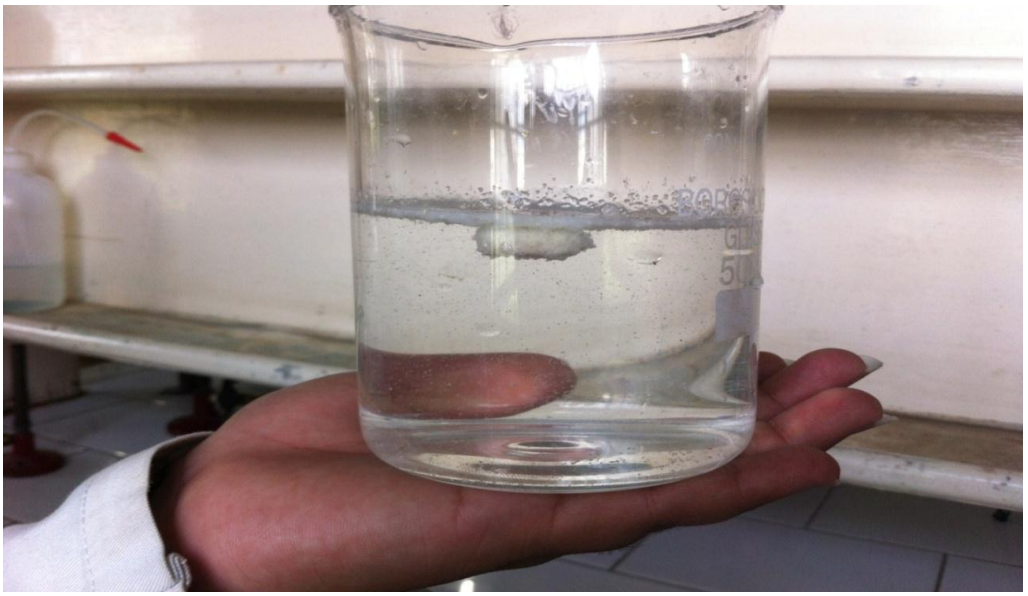


Fig no 9: Floating properties of Azithromycin tablet S2 at 71 sec.

II). Swelling Index

The swelling of the polymers used could be determined by water uptake of the tablet. The complete swelling was achieved at the end of 8hours, therefore percent swelling index was determined at the end of 8hours for all the developed formulations. The values of swelling index of various batches were evaluated as shown in table and

Fig. The swelling index of all the batches was found to be in the range of 86.48 to 98.40%.

Table no. 9: Results of *in vitro* Swelling index of formulation development batches of azithromycin floating tablets.

Formulation code	Swelling index (%)after 8 hours
S1	**93.56**
S2	**98.40**
S3	**88.97**
S4	**86.48**
S5	**90.77**
S6	**88.40**

The swelling index of all the batches was found to be in the range of 86.48 to 98.40%.

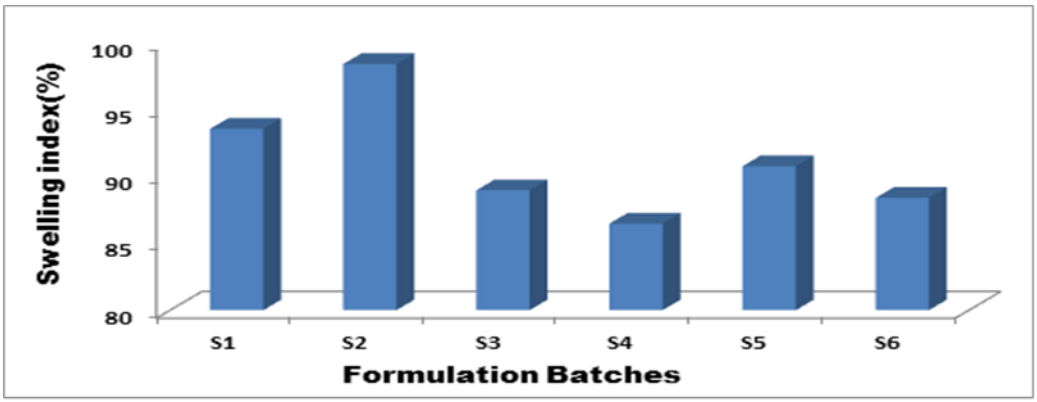


Fig no 10: Swelling index of all the Formulations after 8hours.

Hence from above results the Swelling Index decreases as we increase the number of polymers. The formulation with maximum quantity of HPMC K4M formulation S2 shows the maximum swelling index 98.40%.

III). Dissolution Studies

The dissolution studies were carried out by the procedure has explained earlier. The results of drug release data of all the formulations.

Table 10: In vitro drug release data of formulation S1.

Sl. No.	Time (hrs)	Square root of time	Log time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log Cumulative Percent drug Remaining
1	0	0.0000	-	0	-	100	2.0000
2	2	1.4121	0.301	48.90±1.32	1.689	51.10	1.708
3	4	2.00	0.602	63.21±2.79	1.800	36.79	1.565
4	6	2.44	0.778	80.61±2.97	1.906	19.39	1.287
5	8	2.828	0.903	95.18±4.36	1.978	4.82	0.683

* Average of three determinations

Table 11: In vitro drug release data of formulation S2.

Sl. No.	Time (hrs)	Square root of time	Log time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log Cumulative Percent drug Remaining
1	0	0.0000	-	0	-	100	2.0000
2	2	1.4121	0.301	23.70±2.10	1.374	76.30	1.882
3	4	2.00	0.602	48.65±3.76	1.687	57.15	1.757
4	6	2.44	0.778	52.62±1.99	1.721	51.38	1.710
5	8	2.828	0.903	69.27±4.66	1.840	30.73	1.487
6	10	3.162	1	73.47±3.87	1.866	26.53	1.423
7	12	3.464	1.07	89.71±2.78	1.952	10.29	0.012

* Average of three determinations.

Table 12: In vitro drug release data of formulation S3.

Sl. No.	Time (hrs)	Square root of time	Log time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log Cumulative Percent drug Remaining
1	0	0.0000	-	0	-	100	2.0000
2	2	1.4121	0.301	34.90±2.24	1.542	65.10	1.813
3	4	2.00	0.602	53.75±5.76	1.730	46.25	1.665
4	6	2.44	0.778	65.33±3.87	1.815	34.67	1.539
5	8	2.828	0.903	77.52±3.56	1.889	22.48	1.351
6	10	3.162	1	95.84±4.96	1.981	4.16	0.619

* Average of three determinations.

Table 13: In vitro drug release data of formulation S4.

Sl. No.	Time (hrs)	Square root of time	Log time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log Cumulative Percent drug Remaining
1	0	0.0000	-	0	-	100	2.0000
2	2	1.4121	0.301	35.22±2.54	1.546	64.78	1.811
3	4	2.00	0.602	53.91±1.99	1.731	46.09	1.663
4	6	2.44	0.778	75.96±4.54	1.880	24.04	1.380
5	8	2.828	0.903	91.21±3.65	1.960	8.79	0.943

* Average of three determinations.

Table 14: *In vitro* drug release data of formulation S5.

Sl. No.	Time (hrs)	Square root of time	Log time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log Cumulative Percent drug Remaining
1	0	0.0000	-	0	-	100	2.0000
2	2	1.4121	0.301	27.79±3.43	1.443	72.21	1.858
3	4	2.00	0.602	48.14±2.87	1.682	51.86	1.714
4	6	2.44	0.778	63.30±5.34	1.801	36.70	1.564
5	8	2.828	0.903	78.68±2.76	1.895	21.32	1.328
6	10	3.162	1	93.45±3.12	1.970	6.55	0.186

* Average of three determination.

Table 15: *In vitro* drug release data of formulation S6.

Sl. No.	Time (hrs)	Square root of time	Log time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log Cumulative Percent drug Remaining
1	0	0.0000	-	0	-	100	2.0000
2	2	1.4121	0.301	24.24±1.87	1.384	75.76	1.879
3	4	2.00	0.602	39.08±2.82	1.591	60.92	1.784
4	6	2.44	0.778	52.46±2.97	1.719	47.54	1.677
5	8	2.828	0.903	61.43±3.87	1.788	38.57	1.586
6	10	3.162	1	79.27±4.32	1.899	20.73	1.316
7	12	3.464	1.07	91.80±4.89	1.962	8.20	0.913

* Average of three determinations.

Table 16: Dissolution parameters of formulation development batches.

Batch Code	$t_{50\%}$ (hrs.)	$t_{85\%}$ (hrs.)
S1	2.8	6.7
S2	5.9	11.2
S3	3	8.4
S4	5.6	11
S5	5.7	10.2
S6	5.4	10.6

FT-IR studies of optimized drug formulation

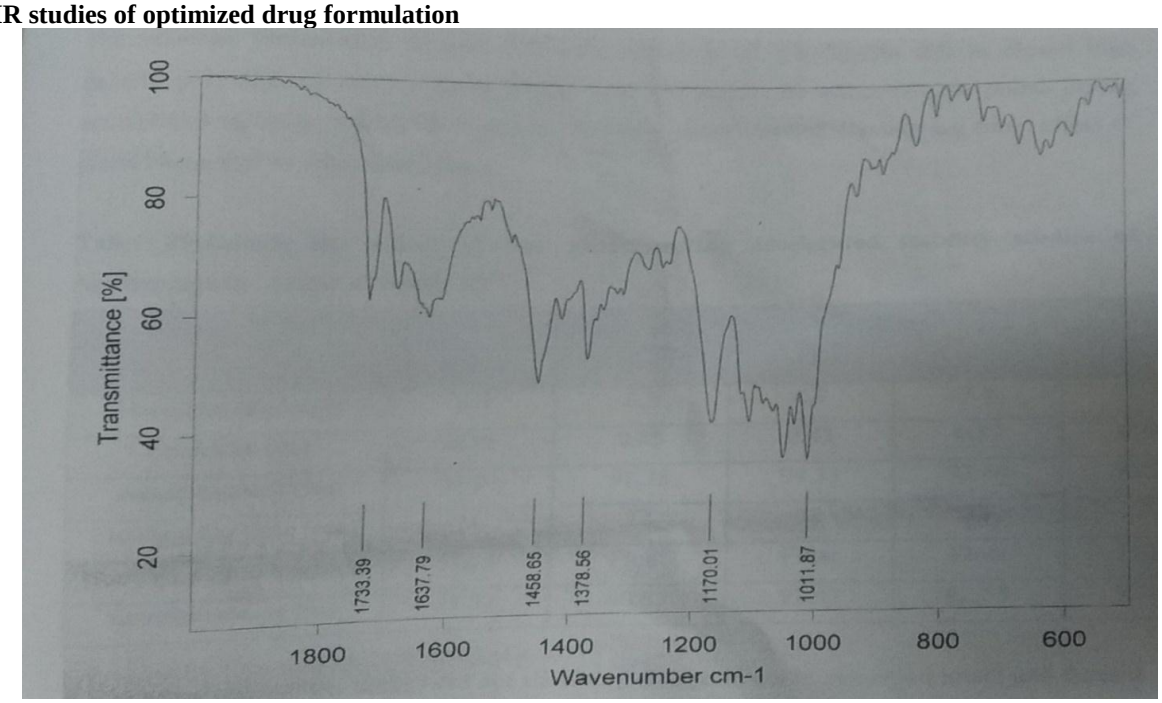


Fig no 11: FT-IR spectra of Final formulation of Azithromycin.

Table 17: Interpretation of FT-IR spectrum Final formulation of Azithromycin.

Infrared Spectrum Data IR Absorption Band(cm-1) (Experimental)	Functional groups
1733	C=O carbonyl ester stretch
1458, 1378	C=O CH_3O & CH_2O alkyl ether stretch
1170, 1101	Symmetric and asymmetric ether stretch

From the above data it was concluded that there is no significant shift(s) in the peaks, indicating no interaction between the drug and the polymers observed in formulation S2. The presence of above peaks confirmed undisturbed drug in the formulation S2. Hence, there was no chemical interaction observed between the drug and the excipients.

Accelerated Stability Studies

The selected formulation tablets (S2) were stored at $40\pm5^0C/70\pm5\%$ RH in closed high density polyethylene bottles for 6 week. Table enlists the effect of time points during accelerated stability studies on hardness, friability, assay content, floating lag time, effect of disturbance and *in vitro* drug release.

Table No 18: Enlists the effect of time points accelerated stability studies of Azithromycin tablet of batch S2.

Parameters	Stability time points				
	0 weeks	1 weeks	2 weeks	4 weeks	6 weeks
Hardness(kg/cm^2)	6.5	6.5	6.9	7.1	7.0
Friability (%)	0.39	0.45	0.43	0.37	0.44
Assay content(%)	93.21	91.78	94.33	93.64	95.21
Floating lag time(sec)	71	72	72	73	75
Buoyancy on disturbing	Float	Float	Float	Float	Float
In vitro release(%)	91.52	90.63	91.53	92.55	93.07

It was observed that the tablets did not show any change in color, remained intact and floated throughout study period. Also the friability and hardness of tablets were well within the range throughout study period. As is evident from the table, the assay drug content was also well within limits (91.78 to 95.21% for selected formulation S2), showing negligible and random variation over time. Thus, it was found that the floating matrix tablets of Azithromycin(S2) were stable under the storage conditions (40±5^{0}C/70±5% RH) for at least 6 week.

CONCLUSION

The effervescent based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel-forming polymers HPMC K4 M, HPMC K100M, Carbopol934 & gas-generating agent sodium bicarbonate was essential to achieve *in vitro* buoyancy. HPMC K 4M alone has resulted in controlled release of drug for 12 hours. *In vitro* dissolution studies showed controlled release of azithromycin for 12 hours, following Higuchi model. The optimized formulation (S2) gives the best results in term of the required floating lag time, floating duration and drug release. From the Formulation Development batches, S2-batch containing azithromycin 250mg, HPMC K4M 200 mg, and sodium bicarbonate 75 mg evolved as the optimized formulation and released more than 85% drug in 11.2 hours. It was observed that in preliminary trials when we formulate the tablets with quantity 500mg the no any formulation show results. The tablets were disintegrate fastly because of large quantity of drug and small quantity of polymer used in the formulations. Thus, the weight of tablet get increased and it were not able to buyont. Hence, the results occur after formulate the tablets of azithromycin with quantity 250mg with different concentrations of polymers. These formulations gave better results. All the formulations showed values within the prescribed limits for tests like hardness, friability, weight variation and drug content indicating that the prepared tablets were of standard quality. FTIR studies of the pure drug, its physical mixture with polymer blend showed that no polymorphic changes occurred during manufacturing of tablets. Accelerated stability studies of selected formulation (S2) indicate that even at extreme conditions, no significant loss in drug assay and dissolution characteristics occured. Conclusively, the results of the current study indicate a promising potential of azithromycin floating drug delivery system as an alternate to the conventional dosage forms.

REFERENCES

1. Hoffman A, Stepensky D, Lavy E, Eyal S, Klausner E, Friedman M. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. Int J Pharm, 2004; 277: 141-153.
2. Sabale V, Sarkarkar S, Pund S, Sabale PM. Formulation and evaluation of floating dosage forms: an overview. Sys Rev Pharm, 2010; 1(1): 33- 39.
3. Jain SK, Awasthi AM, Jain NK, Agrawal GP. Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: preparation and *in vitro* characterization. J Cont Rel., 2005a; 107: 300-309.
4. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. Res J Pharm and Tech., 2008; 1(14): 345-348.
5. Krogel I, Bodmeier R. Development of multifunctional matrix drug delivery system by an impermeable cylinder. J Cont Rel., 1999 a; 61: 43-50.
6. Singh NB, Kim HK. Floating drug delivery system: an approach to oral controlled drug delivery via gastric retention. J Cont Rel., 2000; 63: 235-259.
7. Yeole PG, Khan S, Patel VF. Floating drug delivery systems: need and development. Ind J Pharm Sci., 2005; 67(3): 265-272.
8. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J Cont Rel., 2003b; 90: 143-162.
9. Hwang SJ, Park M, Park K. Gastric retentive drug-delivery systems. Crit Rev Ther Drug Carr Syst., 1998; 15: 243-84.
10. Garg S, Sharma S. Gastroretentive drug delivery systems. Drug Deliv Tech., 2003; 160-166.
11. Chawla G, Gupta P, Koradia V, Bansal AK. Gastroretention: a means to address regional variability in intestinal drug absorption. Pharma Tech., 2003; 27: 50-68.
12. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: a review. AAPS Pharm Sci Tech., 2005; 47: 372-390.
13. Dressman JB, Berardi RR, Dermentzogloss LC, Russell TL, Schmeltz, S.P., Barnett, JL, Jarvenpaa, K.M. Upper gastrointestinal pH in young, healthy men and women. Pharm Res., 1990; 7: 756-61.
14. Desai S, Bolton S. A floating controlled release delivery system: *In vitro* and *in vivo* evaluation. Pharm Res., 1993; 10: 1321-5.
15. Oth M, Franz M, Timmermans J, Moes A. The bilayer floating capsules: a stomach directed drug delivery system for misoprostol. Pharm Res., 1992; 9(3): 298-302.