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HYDRODYNAMICALLY BALANCED TABLETS OF CLARITHROMYCIN: AN APPROACH TO PROLONG AND INCREASE THE LOCAL ACTION BY GASTRIC RETENTION.

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ABSTRACT

Whilst there is keen interest in developing improved drug delivery systems to gastro intestinal tract for treatment of H. pylori induced peptic and duodenal ulcers, in the present study an attempt has been made to develop and evaluate hydrodynamically balanced matrix tablets of clarithromycin which were prepared by using Hydroxypropyl Methylcellulose K4M (HPMC K4M), Hydroxy Propyl Methyl Cellulose K15M (HPMC K15M) and Chitosan with $NaHCO_3$ as gas forming agent. These matrix tablets were evaluated for their physicochemical properties, buoyancy and tablet density. Effect of hardness on matrix tablet revealed that increase in hardness affects buoyancy lag time due to reduction in porosity of compact mass. The release rate determined in 0.1 N HCL (pH 1.2) showed controlled release of drug following non-Fickian mechanism.

Keywords: Clarithromycin; Buoyancy; Swelling index; Gastric residence time.

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INTRODUCTION

Clarithromycin, an advanced generation macrolide antibacterial agents, is first line drug along with amoxicillin and omeprazole for the treatment of *H.pylori* induced peptic and duodenal ulcers [1]. Although *H.pylori* is sensitive to antimicrobial agents *in vitro*, successful treatment of infection is challenging due to its unique characteristics i.e., the bacterium tends to inhabit the gastric mucus gel and hence access for antimicrobial drug to the site of infection is restricted, both from the lumen of the stomach and from the gastric supply [2]. Therefore, one way to improve the efficacy of eradicating *H.pylori* infection is to deliver the antibiotic locally to stomach. This goal can be achieved by the development of hydrodynamically balanced system, which prolong the gastric residence time, decreases the diffusional distance and allow more of the antibiotic to penetrate through gastric mucus layer and act locally at the infection site [3].

Hydrodynamically balanced systems are modified dosage forms which aim to prolong release and restrict the region of drug delivery to stomach utilizing floating behavior [4]. The objective of present study was an approach to develop and evaluate hydrodynamically balanced matrix tablets of clarithromycin using hydroxylpropyl methylcellulose and chitosan, to retain the tablets in the stomach by using sodium bicarbonate as gas-forming agent to achieve enhanced gastric residence time.

MATERIALS AND METHODS

Clarithromycin was obtained from Cipla Research and Development., Vikroli. Two grades of hydroxylpropyl methylcellulose (HPMC Methocel K4M, HPMC Methocel K15M) were obtained from Colorcon Asia Pvt Ltd., Verna. Chitosan was procured from Central Institute of Fisheries Technology., Cochin. Lactose and magnesium stearate from Loba chemicals., Mumbai. All other ingredients were of analytical grades and used as procured.

I.R. Studies

It is one of the most powerful analytical technique for chemical identification of drug. The pure drug and its formulation were subjected to IR studies. In present study, the potassium bromide disc (pellet) method was employed.

Preparation of hydrodynamically balanced tablets

Hydrodynamically balanced tablets of clarithromycin were prepared by direct compression method using different grades of hydroxypropyl methylcellulose (HPMC MK4M, HPMC MK125M) and chitosan along with sodium bicarbonate as gas generating agent. Table I shows formulation composition. All the ingredients except magnesium sterate were blended in glass mortar uniformly. After sufficient mixing of drug as well as other components, magnesium stearate was added and further mixed for additional 2-3 min. The tablets were compressed

using 13 mm single punch hydraulic press. In all five batches formulated the quantity of polymer and gas generating agent was kept constant.

Evaluation of hydrodynamically balanced tablets

Powder blend prepared for direct compression was evaluated for flow properties. Tablets prepared were evaluated for hardness and friability using Monsanto hardness tester and Roche friabilator respectively. Thickness, compatibility of drug with polymer, buoyancy lag time, duration of floating, density of tablets, effect of hardness on buoyancy lag time and *in vitro* drug release characteristics were also studied.

Buoyancy determination

The time between introduction of dosage form and its buoyancy in the simulated gastric fluid i.e. 0.1 N HCL and duration of buoyancy (total floating time) was measured. Tablet was introduced in beaker containing simulated gastric fluid. The time taken for dosage form to emerge on the surface of medium is buoyancy lag time and total duration of time by which dosage form remains buoyant is known as total floating time.

Tablet density

Tablet density is an important parameter for hydrodynamically balanced tablets as the tablets will float only when its density is less than that of gastric fluid (1.004) Density of the tablet was determined by using relation [5].

$$V=\pi r^2 h$$

$$d= m/v$$

v= volume of tablet (cc), r= radius of tablet (cm), h= crown thickness of tablet (g/cc), m= mass of tablet.

***In vitro* drug release study**

Paddle type dissolution apparatus with rotation speed of 50rpm was used for study. The tablets were placed in ring mesh to retain it at bottom in 900ml 0.1 N HCL. 1ml of sample was withdrawn regularly from the dissolution vessel at hourly interval up to 10h, analyzed spectrophotometrically at 203 nm using Shimadzu 1601 UV/ Vis spectrophotometer, and at the same time equal amount of fresh dissolution medium was replaced. The rate and mechanism of drug release from prepared matrix tablets was analysed by fitting dissolution data into Zero-order,Higuchi and Korsemeyer Peppas model. The promising formulation was compared with marketed product (Clarithro ER 500mg) formulation for drug release study.

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RESULTS AND DISCUSSIONS

I.R studies of pure drug and formulations showed same characteristics peaks of drug indicating no interaction of drug with formulation components fig I-VI. The compressibility index for all formulations was found to be in the range 15%-16% and angle of repose between 24^0 to 29^0. These values indicate good flow property of the powder blend with HPMC and Chitosan.

The formulated matrix tablets were round and flat in shape with a diameter of 13 mm, thickness in the range of 5.12 mm to 5.18 mm, and hardness ranged from 4.1 kg/cm^2 to 4.5 kg/cm^2. Percentage friability of all formulations was in between 0.72%- 0.96%. Values of hardness and percent friability indicate good handling property of the prepared tablets.

On immersion in 0.1N HCL (pH-1.2) at 37±2^o C, formulation F_2 containing HPMC K15 M showed buoyancy lag time of 49 sec. The formulation containing chitosn alone and in combination with HPMC K15M showed highest buoyancy lag time and total floating time of less than 12 hours Table II. This may be due to insufficient entrapment of gas inside the gelatinous layer which may lead to variations in buoyancy lag time and total floating time fig-VIII.

Study revealed that prepared tablets have density less than that of gastric contents (1.004 g/cm^3). When the tablets come in contact with the test medium, they expanded (because of swellable polymers) and there was liberation of CO_2 gas (due to effervescent agent, $NaHCO_3$). The density decreased due to this expansion and upward force of CO_2 gas (due to effervescent agent, $NaHCo_{3)}$. Which plays an important role in ensuring the floating capability of dosage form. Effect of hardness on buoyancy lag time of batch F2 showed that increase in hardness results in an increase in the buoyancy lag time. The compression pressure resulted in reduction of porosity of the tablet and moreover, the compacted hydrocolloid particles on the surface of the tablet cannot hydrate rapidly when the tablet reaches the gastric fluid and as a result of this, the capability of the tablet to float is significantly reduced. Plot of buoyancy lag time (sec) v/s hardness (kg/cm^2) is depicted in fig –VII.

For *in vitro* release study tablet was placed in ring mesh device as described by Fassihi. *et al* [6]., because it was reported that when paddle apparatus was used, the tablets would rise and eventually stick to the flange of the rotating shaft which results in partial surface occlusion. In case of basket apparatus, it ensures full exposure of all surfaces of hydrophilic swelling tablets, but after 5 – 7 hours the tablets swell, to such an extent that they were completely constricted by the radius of the basket, and the tablet was unable to swell further and move in unimpeded fashion leading to limited drug release. In order to overcome these drawbacks ring mesh device was employed in the study.

From the *in vitro* dissolution data it was found that formulation F4 containing chitosan alone released 97.2% of drug within 6 hours of study indicating that polymer amount was not sufficient to control the drug release. Formulation F5 containing chitosan along with HPMC

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showed better control of drug release than chitosan alone, i.e 96.3% drug release at end of 10 hours. Tablets of batch F1, F2, F3 contained same amount of polymer of different grades viz, HPMC K4M, HPMC K15M and combination of both the polymers, which showed drug release rate of 93.6%, 89.4% and 91.8% respectively Table III. Amongst all formulations studied controlled release was best observed in formulation F2 containing HPMC K15M. The kinetic studies revealed that drug release best fitted in Korsemeyer Peppas model, 'n' values lies between 0.5 – 1.0 indicating that the release followed non – Fickian diffusion i.e., by both diffusion and polymer chain relaxation mechanism. Plot of % drug release vs. Time (hr) is depicted in fig IX. The marketed product gave 92.38% of drug release in 10 hrs of dissolution study. *In vitro* dissolution profile of marketed product in comparison to the formulated formulation F2 showed 89.4% of drug release which has better control over release of drug in comparison to marketed product fig X.

CONCLUSION

It is evident from this study that controlled release hydrodynamically balanced tablets of clarithromycin can be prepared successfully by incorporating sodium bicarbonate as gas generating agent in HPMC K15M facilitating local action due to prolonged residence time in stomach.

ACKNOWLEDGEMENT

Authors thanks K.L.E.S's College of Pharmacy, Belgaum for providing the necessary facilities and help in carrying out this study.

TABLE I: COMPOSITION OF HYDRODYNAMICALLY BALANCED MATRIX TABLETS OF CLARITHROMYCIN.

Ingredients (mg/tab)	F1	F2	F3	F4	F5
Clarithromycin	500	500	500	500	500
HPMC K4M	200	-	100	-	-
HPMC K15M	-	200	100	-	100
Chitosan	-	-	-	200	100
Sodium Bicarbonate	80	80	80	80	80
Lactose	10	10	10	10	80
Magnesium Streate	10	10	10	10	10

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TABLE II: TABLET DENSITY, BUOYANCY LAG TIME, FLOATING TIME.

Batch	Tablet Density (g/cc) n=1	Buoyancy Lag Time (sec)` n=1	Total Floating Time (hrs) n=1
F1	0.93	62 sec	> 12 hrs
F2	0.82	49 sec	> 12 hrs
F3	0.89	55 sec	> 12 hrs
F4	0.99	134 sec	> 06 hrs
F5	0.97	102 sec	> 10 hrs

n= 1 tablet

TABLE III: CUMULATIVE % DRUG RELEASED FROM TABLET FORMULATIONS F1 TO F5 AND MARKETED PRODUCT.

Time (hrs)	F1 n=3	F2 n=3	F3 n=3	F4 n=3	F5 n=3	Marketed Product n=3
1	22.5±1.15	20.7±1.1	21.6±2.02	25.2±1.4	23.4±1.2	24.3±1.35
2	32.4±0.86	31.5±1.9	33.3±1.2	48.6±0.4	38.7±1.4	34.2±2.89
3	49.5±1.78	46.8±0.3	47.7±0.30	59.4±0.45	57.6±2.3	48.6±2.12
4	58.5±2.8	53.1±0.54	56.7±1.3	67.5±0.6	61.2±0.4	59.4±0.56
5	70.2±1.9	62.1±0.44	64.8±1.45	81.9±2.4	71.1±1.1	66.6±0.23
6	75.6±2.2	68.4±2.2	69.3±1.90	97.2±2.9	77.4±2.2	74.7±0.98
7	80.1±1.9	73.8±2.05	76.5±1.23	--	85.5±0.3	78.9±0.25
8	83.7±1.5	78.3±0.42	79.2±1.78	--	88.2±0.65	81.9±0.12
9	91.8±2.5	84.3±0.9	87.3±2.25	--	92.7±1.2	90.7±0.98
10	93.6±2.2	89.4±0.6	91.8±2.11	--	96.3±0.76	92.3±1.11

n=3 tablets

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FIG I: IR SPECTRA OF CLARITHROMYCIN

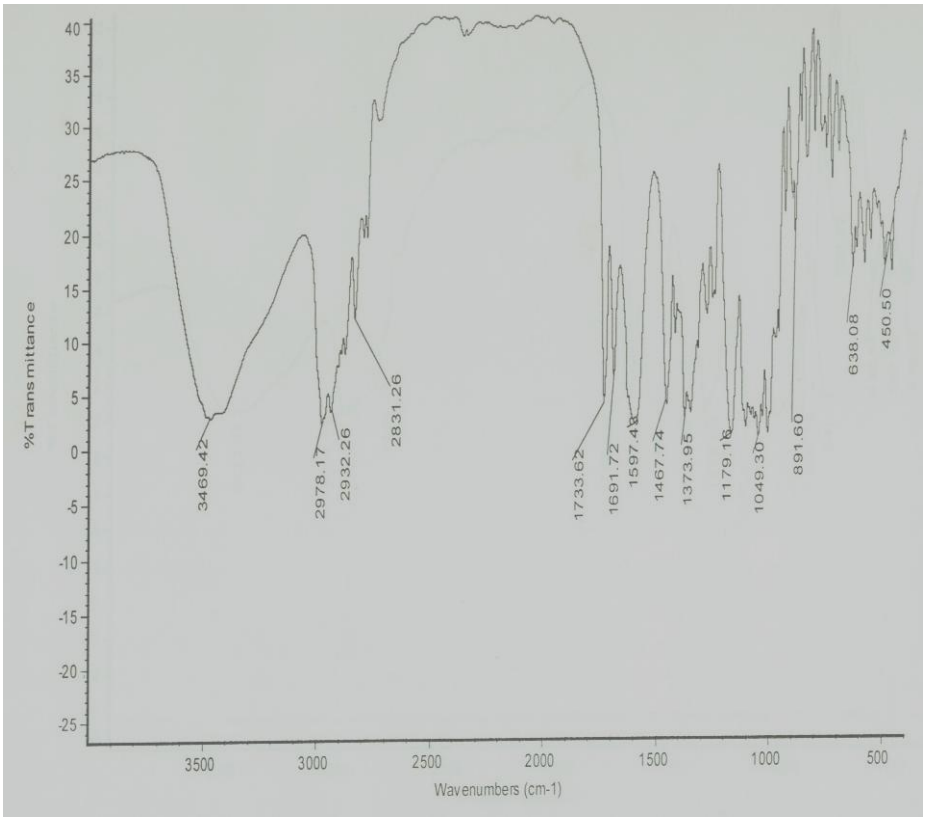

FIG II: IR SPECTRA OF FORMULATION F1

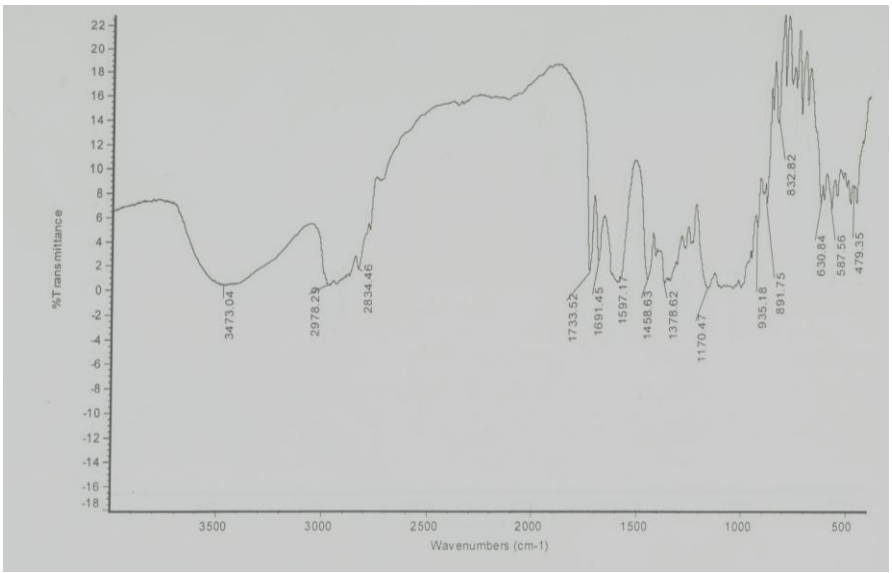

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FIG III: IR SPECTRA OF FORMULATION F2

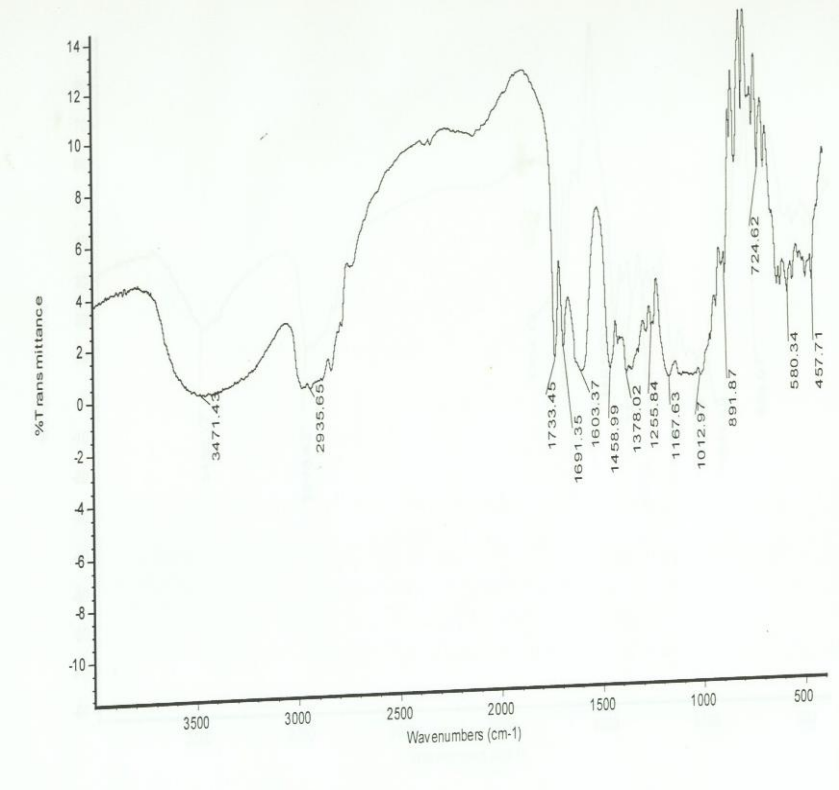

FIG IV: IR SPECTRA OF FORMULATION F3

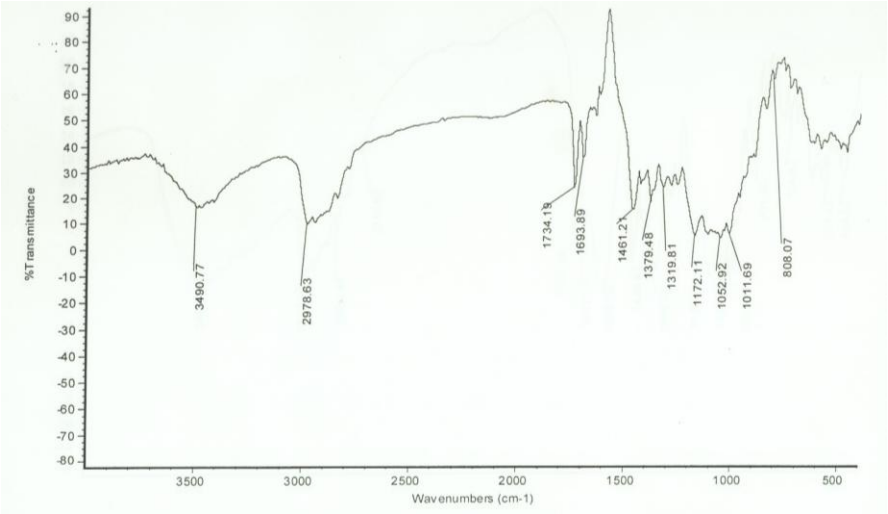

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FIG V: IR SPECTRA OF FORMULATION F4

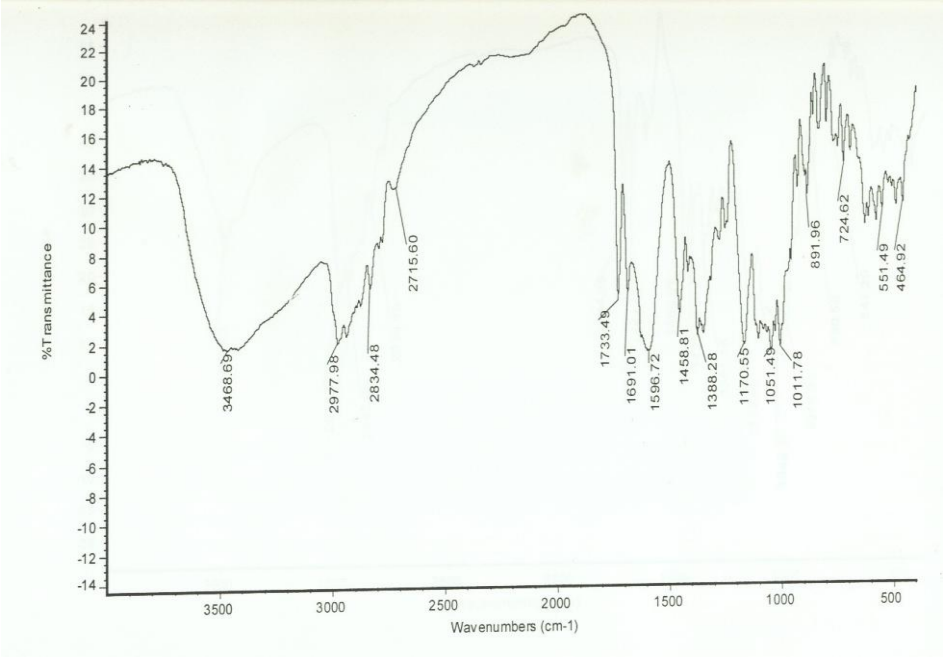

FIG VI: IR SPECTRA OF FORMULATION F5

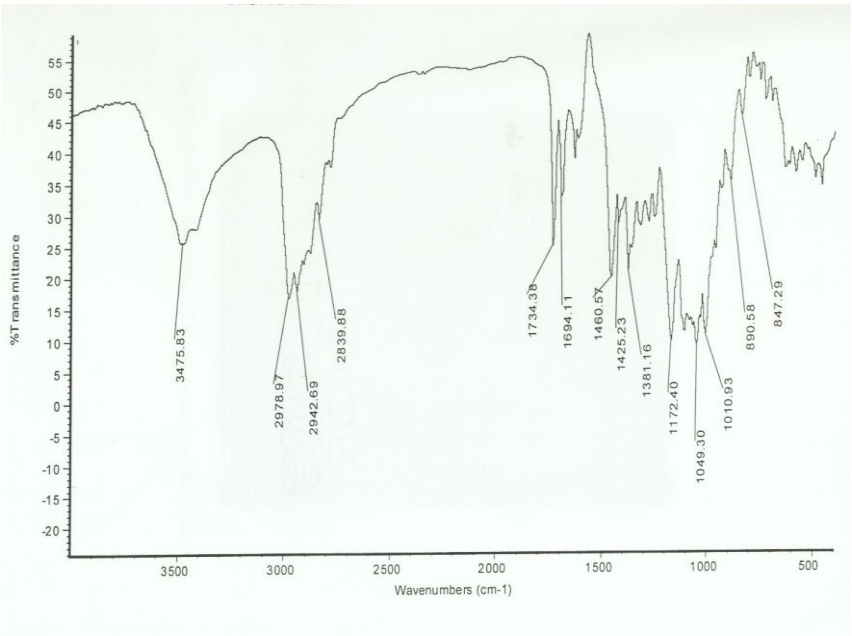

FIG.VII: EFFECT OF HARDNESS ON BUOYANCY LAG TIME OF BATCH F2

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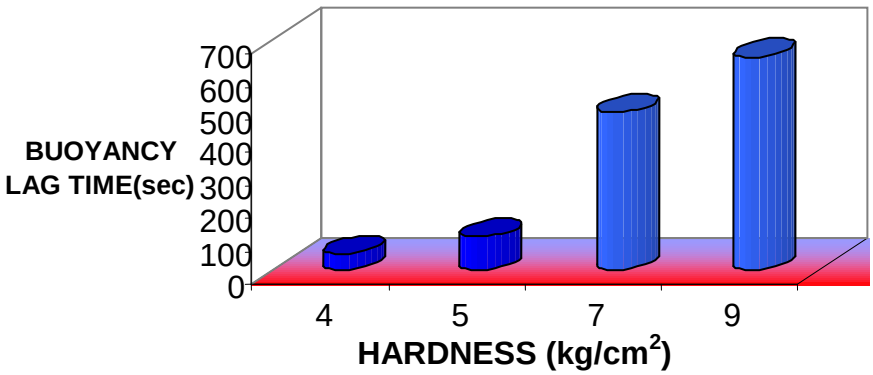

FIG VIII: *IN VITRO* BUOYANCY CHARACTERISTIC OF THE TABLET

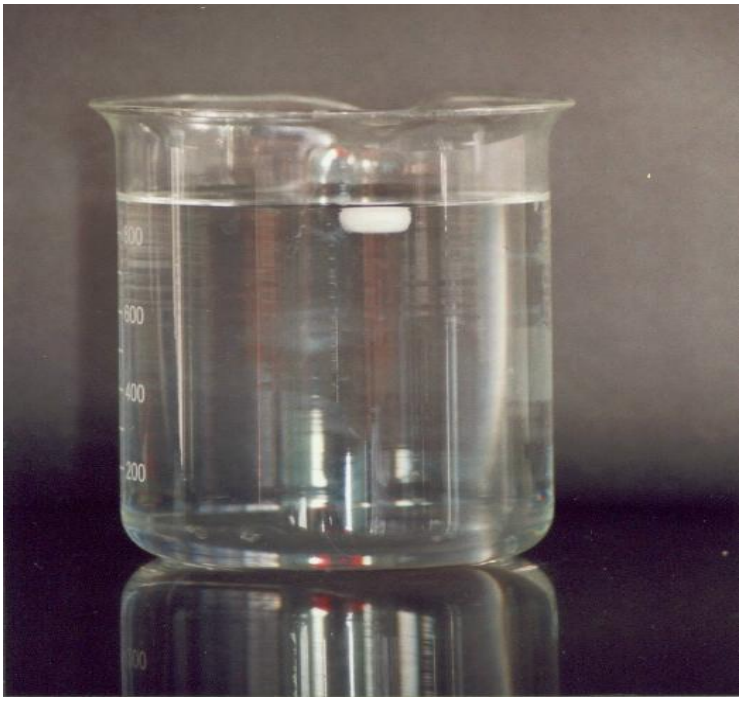

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FIG IX: *IN VITRO* DISSOLUTION PROFILE FOR TABLETS OF BATCH F1 TO F5

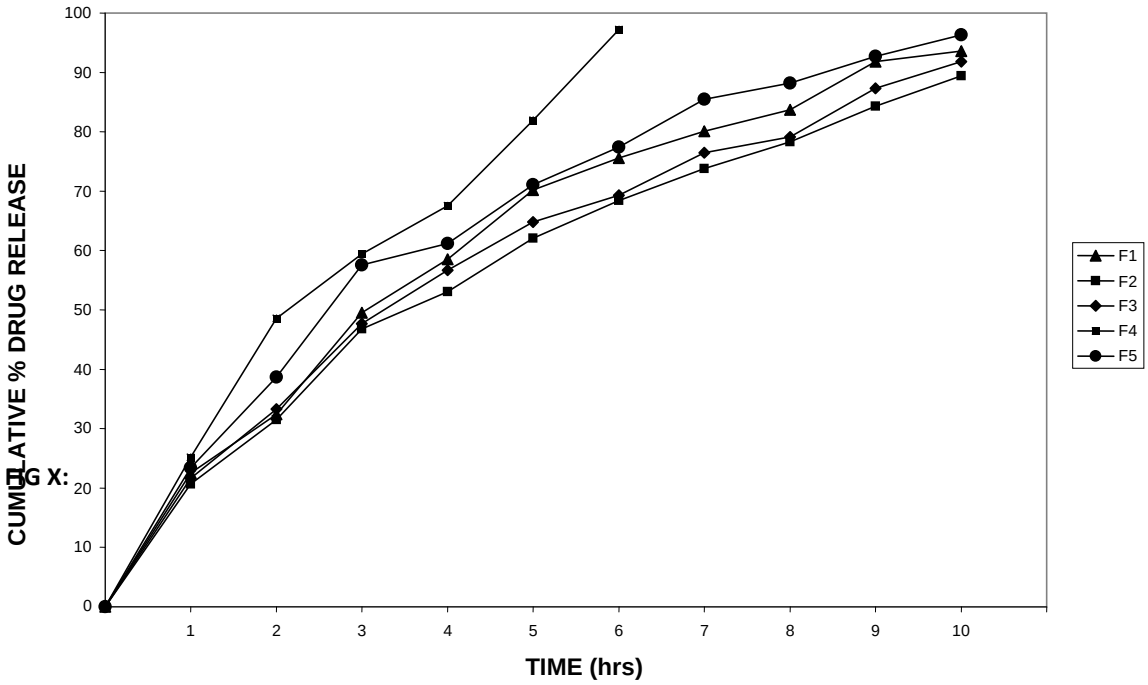

FIG X:

FIG X: COMPARISION OF *IN VITRO* RELEASE PROFILE OFFORMULATION F2 AND MARKETED DRUG (MP)

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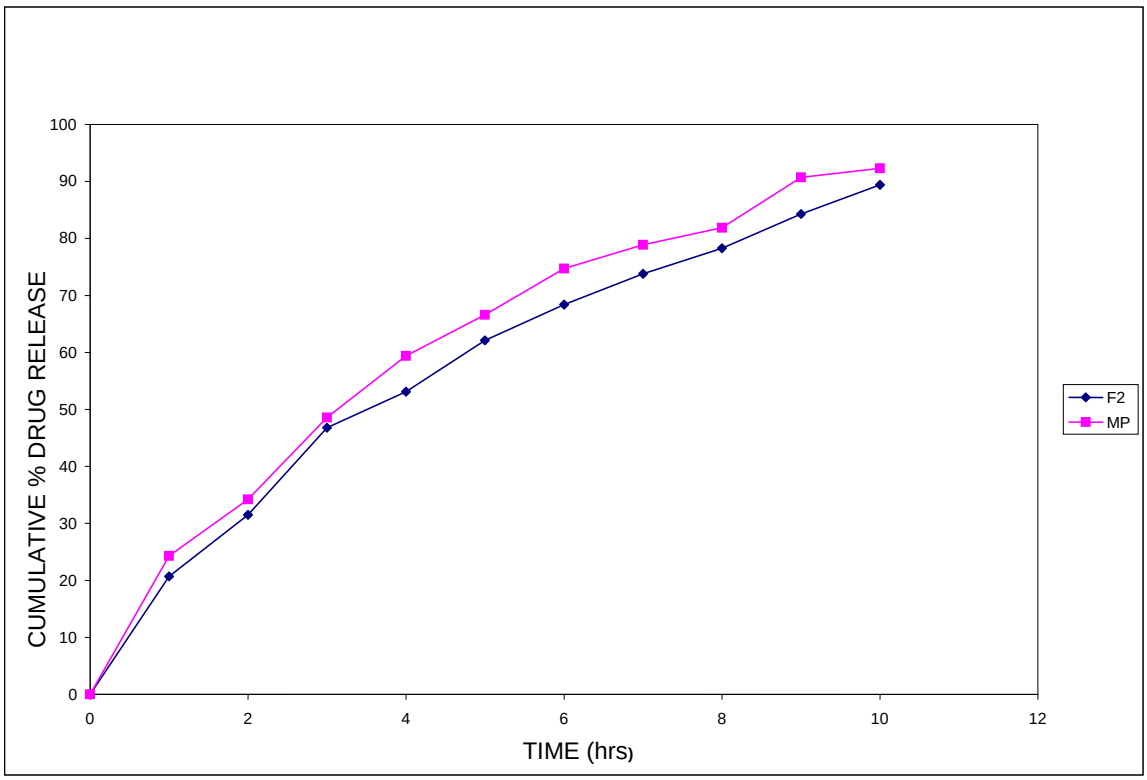

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