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FORMULATION AND *IN VITRO* EVALUATION OF METOPROLOL SUCCINATE FLOATING TABLETS BY USING TWO VISCOSITY GRADE OF HPMC

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ABSTRACT

Metoprolol is a beta$_1$-selective (cardio selective) adrenergic receptor blocking agent used in the treatment of Hypertension. The purpose of this investigation is to improve bioavailability by preparing a gastroretentive drug delivery system. Floating tablets of Metoprolol Succinate were prepared by employing two different grades of HPMC K4M and HPMC E15M in different concentrations by effervescent granulation technique. These grades of HPMC K4M and HPMC E15M were evaluated for their gel forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. The tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy and dissolution studies. The prepared tablets exhibited satisfactory physicochemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The tablet swelled radially and axially during *in vitro* buoyancy studies. It was observed that the tablet remained buoyant for 6-8 hours. A combination of 5:1 sodium bicarbonate and magnesium stearate was found to achieve optimum *in vitro* buoyancy. The tablets with HPMC K4M and HPMC E15M with drug in the ratio of 1:1:2 were found to float for longer duration and released found to be 98.98%. FTIR show that there is no interaction with drug and other excipients. Selected Formulation F4 were subjected to FTIR that shows that is compatible and release was found superior to marketed conventional tablets with respect to floating and found to be stable.

INTRODUCTION [1-6]**:** Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site-specific delivery, oral dosage forms have really progressed. However, it is a well-accepted fact that it is difficult to predict the real *in vivo* time of release with solid.

Gastric emptying of dosage form is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage form.

In such circumstances, prolonged gastric retention is important in achieving control over the gastric retention time (GRT) because this helps to retain the CR system in the stomach for a longer and predicted time. In addition, this improves the bioavailability of the basic drug that has poor solubility in higher pH and drugs having narrow absorption window (Upper part of GIT).

Gastroretentive Drug Delivery System [7]:

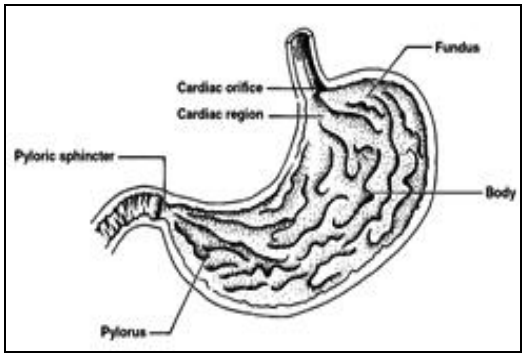

FIG 1: VIEW OF GASTROINTESTINAL TRACT

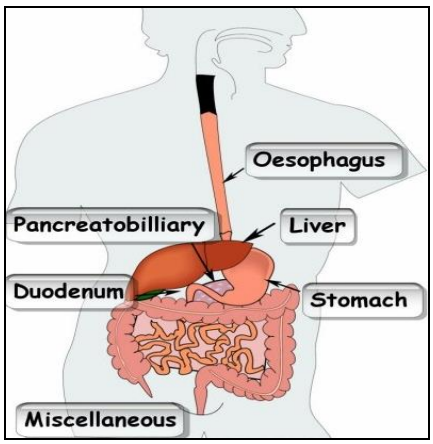

FIG. 2 ANATOMY OF STOMACH

Various approaches in Gastroretentive Systems [7]: Dosage forms with a prolonged GRT, i. e. gastro-remaining or gastroretentive dosage forms (GRDF) will bring about new and important therapeutic options. For instance, they will significantly extend the period of time over which drugs may be released, and thus prolong dosing intervals and increase patient compliance beyond the compliance level of existing controlled release dosage forms. Many of today's so-called "Once-a-day" formulations will become replaced by products with release and absorption phases of approximately 24 hours.

Also, GRDF will greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at the gastric mucosa which are sustained over a long period of time. For example, the eradication of *Helicobacter pylori,* which today requires the administration of various medications several times a day according to a complicated regimen and which frequently fails as a result of insufficient patient compliance, could perhaps be achieved more reliably using GRDF to administer smaller drug doses fewer times.

Finally, GRDF will be used as carriers for drugs with so called absorption windows: these substances are taken up only from very specific sites of the gastrointestinal mucosa, often in a proximal region of the small intestine. Conventional controlled release dosage forms pass the absorption window while they still contain a large and rather undefined portion of the dose which is consequently lost for absorption. In contrast, an appropriate GRDF would slowly release the complete dose over its defined GRT and thus, make it continuously available to the appropriate tissue regions for absorption.

MATERIALS AND METHODS:

Materials: Metoprolol succinate Obtained as a gift sample from Gift sample supplied by Emami Pvt. Ltd. Kolkata, Chloroform, Sodium bicarbonate and Ethanol obtained as a Gift sample supplied Merck specialties Pvt. Ltd., Magnesium stearate and Poly vinyl pyrolidone (K30) Obtained as a Loba Chem. Pvt. Ltd, Mumbai, Hydroxyl propyl methyl cellulose (k4m) and Hydroxyl propyl methyl cellulose (E15m) Obtained as a Gift sample Loba Chem. Pvt. Ltd, Mumbai

Methods:

1. **Preparation of Floating Tablets of Metoprolol Succinate:** The manufacture of granulation for tablet was prepared by wet granulation method. This is the most widely and general method used in the preparation of tablet. This method is popular because the granulation meets all the quantities required some good tablets. The step involved on the wet method are weighing, mixing, granulation, screening the damp mass drying, dry-screening, lubrication and compression (**table 1**).

2. **Procedure:** First an accurately weighed all quantity of drug, excipient, and polymers like (DrugMetoprolol succinate, HPMC (K4M, E15M), $NaHCO_3$.) They were mixed thoroughly with the help of mortor pastel. Then weighed magnesium stearate and pvp. PVP was taken in a small petridish and taken 3ml ethanol and putted into it and shaked. After mixed PVP and ethanol. Then all the ingredients were added with PVP and Ethanol in a small petridish. Then mixed all the ingredient thoroughly. After mixed all the ingredients were prepared the damp mass. Damp mass is then

passed through sieve no- 1mm for granulation. Then dried the wet granules at 60°C for 30-45 minutes. After dried the lubricant (Mg. stearate) was added and mixed very well. After that granules were compressed by single punch cadmach tablet compression machine with 12mm punch.

TABLE 1: COMPOSITION OF FLOATING TABLETS OF METOPROLOL SUCCINATE

Ingredients (mg per tablet)	Formulation Code						
	F1	F2	F3	F4	F5	F6	F7
Metoprolol Succinate	100	100	100	100	100	100	100
HPMC K4M	95	7.5	46.25	50	92.5	92.5	72.5
HPMC E15M	-	92.5	46.25	50	3.75	7.5	22.5
Sodium bicarbonate	30	25	32.5	25	28.75	25	30
Magnesium stearate	5	5	5	5	5	5	5
PVP K-30	20	20	20	20	20	20	20
TOTAL	250	250	250	250	250	250	250

Method of preparing the Standard Curve: An accurately weighed 100mg of pure drug **(Metoprolol succinate)** was taken in a clean dry container. In a clean 100ml of volumetric flask the drug was placed. Volume is make upto accurately 100ml to the volumetric flask, by using the solvent 0.1N HCl. And shake slowly for few times. Allow the drug to dissolve in the 0.1N HCl. This solution gives the concentration 1000 µg/ml. Then 10ml of the above solution was pipetted out into a 100ml of a another volumetric flask and made the volume upto 100ml with 0.1N HCl to give the stock solution of concentration 100mg/ml.

Working Standard solution: Take 0.5 ml, 1 ml, 1.5 ml, 2 ml, 2.5 ml, 3 ml, 3.5 ml, 4 ml, 4.5 ml, 5ml of the solution respectively in each of this into a individual 25ml of volumetric flask. The volume is make upto accurately 25ml. From the stock solution different concentration of solution was taken like 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, 12 µg/ml, 14 µg/ml, 16 µg/ml, 18 µg/ml, 20µg/ml.

Procedure of Standard Plot: Various concentrations were prepared by suitable diluting working standard solution were measured at 222 nm using U.V.Visible spectrophotometer. Then, the standard plot of Absorbance vs. Concentration was drawn the data show in **table 2**.

TABLE 2: STANDARD CURVE OF METOPROLOL SUCCINATE

Concentration in µg/ml	Absorbance at 222 nm
2	0.064
4	0.126
6	0.184
8	0.241
10	0.3
12	0.366
14	0.419
16	0.482
18	0.538
20	0.607

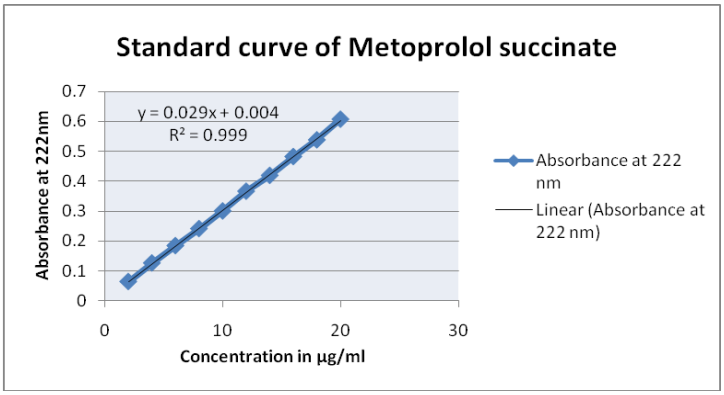

FIG. 3: STANDARD CURVE OF METOPROLOL SUCCINATE

RESULTS AND DISCUSSION

Flow properties:

A. Angle of Repose: This was measured according to the fixed funnel method. A funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip 2.5 cm height (h), above graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. The mean diameter (2r) of the powder cone was determined and the angle of repose of the powder material was calculated using the formula.

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

Where, h is height of the pile, and r is radius of the pile. The test was repeated thrice.

Relationship between powder flow and angle of repose:

Angle of repose	Type of flow
< 20	Excellent
20-30	Good
30-34	Passable
> 40	Very poor

B. Apparent Bulk Density: The bulk density, as a measure used to describe packing materials or granules, was determined by transferring the accurately weighed amount of agglomerates to the graduated cylinder (10 ml) with the aid of a funnel. The volume was noted and apparent bulk density was determined as the ratio of weight of the sample to the volume occupied. The test was repeated thrice.

C. Tapped Density: Weighed quantity of agglomerates, was transferred to a 10 ml graduated cylinder and tapped using tapped density apparatus for a fixed number of taps (100). The volume was noted and tapped density was determined as the ratio of weight of sample to tapped volume. Average of three determinations was taken.

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

D. Hausner's Ratio: Hausner's ratio is an indication of the flowability of powder and the ratio is greater than 1.25 is considered to be an indication of poor flowability. Hausner's ratio was determined by the following equation. The test was done in triplicate.

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

E. Carr's Index: Flowability of untreated and agglomerated samples was also assessed from Carr's Index (CI) The compressibility of sample blend was determined from their apparent bulk density and the tapped densities by using the following formula. The test was carried out in triplicate.

$$\% \text{ Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Flow Properties of Granules: The granules prepared for compression of floating tablets were evaluated for their flow properties (**Table 3**). Angle of repose, Bulk density, Tapped density and Hausner ratio ranged from granules of different formulations. These values indicate that the prepared granules exhibited good flow properties.

Evaluation of Tablet [8, 9]:

1. **Weight Variation:** Twenty tablets were randomly selected from each batch individually weigh, the average weight and standard deviation of 20 tablet calculated (Krishanaiah et al., 2003) **(Tablet 4).**

2. **Thickness:** The thickness of the tablet was measured by using digital venire caliper, twenty tablets from each batch were randomly selected and thickness was measured (The British Pharmacopoeia, 2005) **(Table 4).**

3. **Hardness:** Hardness was measured using Pfizer hardness tester, for each batch three tablets were tested (The United State of Pharmacopoeia, 1995). **(Table 4).**

4. **Friability:** Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted and weighted (Chaudhari PD, 2005) **(Table 4).**

5. **Drug Content Uniformity:** Ten tablets were randomly selected and allowed to equilibrate with Hcl acid buffer of pH 1.2 overnight and the solution was filtered (0.22 µ, Millipore) after 24 hours. Suitable dilutions were made with Hcl acid buffer of pH 1.2 to get the concentration in Beer's range. Absorbance of the solution was analyzed spectrophotometrically at 280nm against suitable blank using UV-visible spectrophotometer (1800, Shimadzu, Kyoto, Japan) and drug content per tablet was calculated **(Table 4).**

6. ***In-vitro* Dissolution Study:** Dissolution study was carried out using USP dissolution test apparatus type II. The dissolution medium used was 900 ml of 0.1N HCl buffer at 37±0.5^{o}C. The paddle speed was kept at 50 rpm throughout the study. Aliquot of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume. After each sampling, suitably diluted with 0.1N HCl buffer and analyzed spectrophotometrically at 277nm against suitable blank using UV-Visible spectrophotometer (1800, Shimadzu, Kyoto, Japan) **(Table 5, 6 and Fig. 4).**

TABLE 3: FLOW PROPERTIES OF GRANULES

Code	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner ratio (HR)	Carr index (IC)
F1	26.528±0.235^0	0.541±0.032	0.634±0.043	1.154	0.119
F2	28.512±0.290^0	0.538± 0.045	0.660 ±0.057	1.167	0.145
F3	26.210±0.352^0	0.547± 0.058	0.652±0.083	1.125	0.141
F4	29.050±0.252^0	0.598± 0.026	0.674±0.048	1.178	0.176
F5	28.625±0.374^0	0.548± 0.048	0.660±0.061	1.156	0.154
F6	28.561±0.380^0	0.565± 0.043	0.651±0.053	1.134	0.148
F7	29.653±0.784^0	0.589±0.086	0.662± 0.049	1.170	0.173

TABLE 4: PHYSICO-CHEMICAL CHARACTERIZATION OF METOPROLOL SUCCINATE FLOATING TABLETS

Code	Uniformity of Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (mg)	Floating lag time (sec.)	Total floating time (hr)
F1	±1.309	2.7±0.229	0.45 ± 0.16	85.911	8	More than 8
F2	±6.250	2.8 ±0.304	0.41 ± 0.09	86.329	8	4
F3	±6.713	2.6±0.19	0.43 ± 0.10	95.004	9	More than 8
F4	±2.712	3.0±0.133	0.39 ± 0.12	90.614	6	More than 8
F5	±3.739	3.1±0.097	0.36 ± 0.04	87.27	15	More than 8
F6	±2.434	3.1±0.119	0.28 ± 0.14	96.049	30	More than 8
F7	±2.251	2.6±0.198	0.34 ± 0.09	97.826	28	More than 8

TABLE 5: *IN VITRO RELEASE* OF METOPROLOL SUCCINATE FLOATING TABLETS

Time in Hr.	Formulation Code						
	F1	F2	F3	F4	F.5	F6	F7
0.5	15.240	28.416	14.732	15.446	18.625	19.586	15.076
1	23.474	42.363	24.712	24.249	30.352	23.660	28.153
2	37.664	66.421	35.960	39.197	44.665	39.173	43.230
3	50.102	92.571	48.633	48.830	58.634	53.431	57.076
4	61.664	----	60.198	62.117	69.844	64.087	67.692
5	69.197	----	71.445	73.7439	81.053	74.428	78.923
6	78.832	----	81.267	82.380	96.402	83.046	86.461
7	87.240	----	89.346	92.0138	----	91.978	92.769
8	95.824	----	93.940	98.989	----	96.992	98.307

TABLE 6: *IN VITRO* RELEASE OF SELECTED FLOATING TABLETS OF METOPROLOL SUCCINATE (F4) AND MARKETED PRODUCT

Time in (Hr)	F4 % Drug Released	Marketed tablet % Drug Released
0.5	15.446	18.787
1	24.249	23.457
2	39.197	39.415
3	48.830	52.413
4	62.117	63.015
5	73.743	73.488
6	82.380	83.049
7	92.0138	91.972
8	98.989	99.589

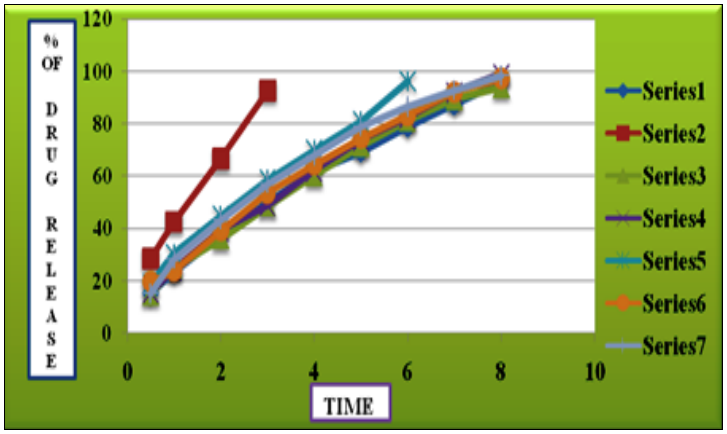

FIG. 4: *IN VITRO RELEASE* OF METOPROLOL SUCCINATE FLOATING TABLETS

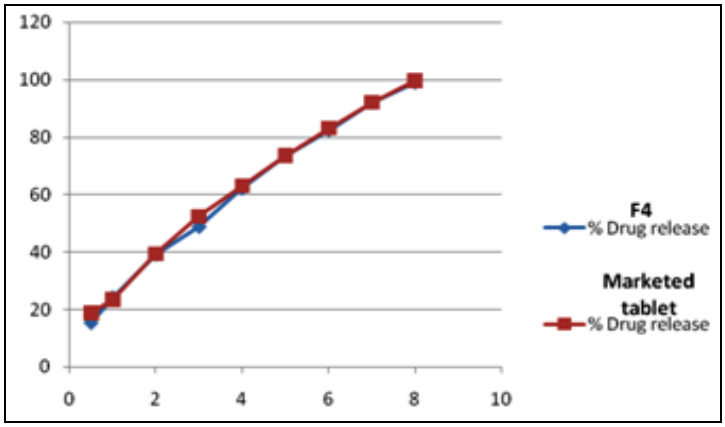

FIG 5: *IN VITRO* RELEASE OF SELECTED FLOATING TABLETS OF METOPROLOL SUCCINATE (F4) AND MARKETED PRODUCT

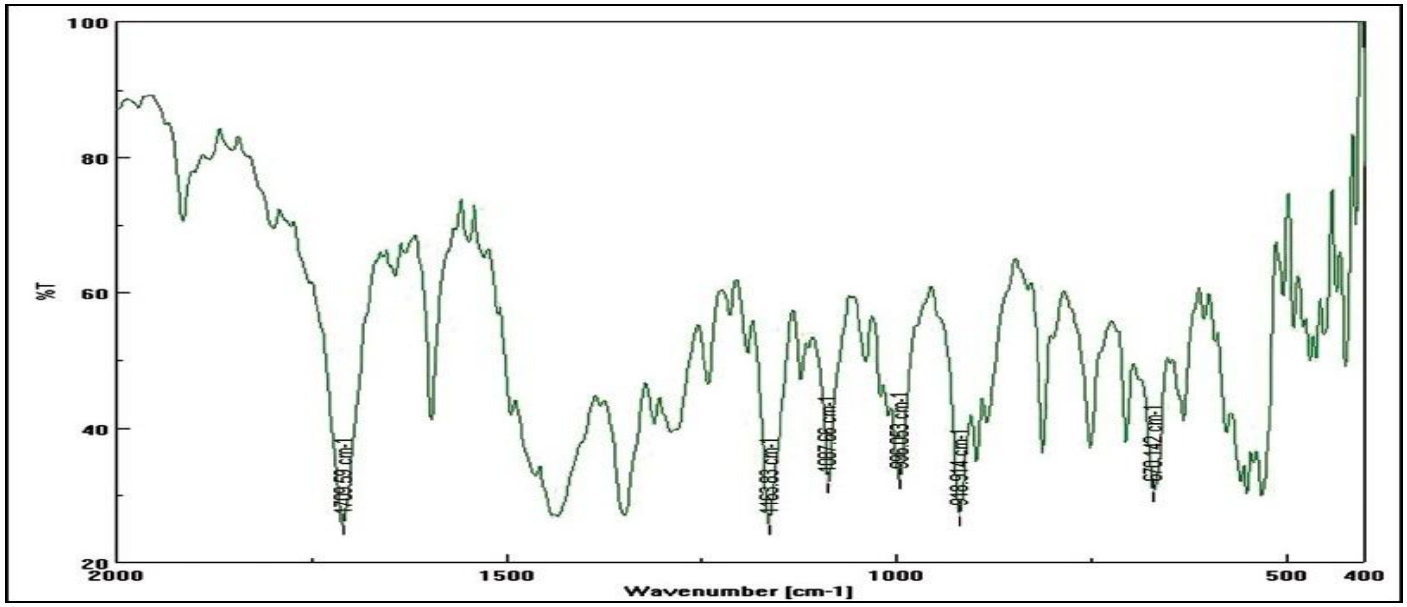

FIG. 6: FTIR SPECTRUM OF METOPROLOL SUCCINATE HCl PURE

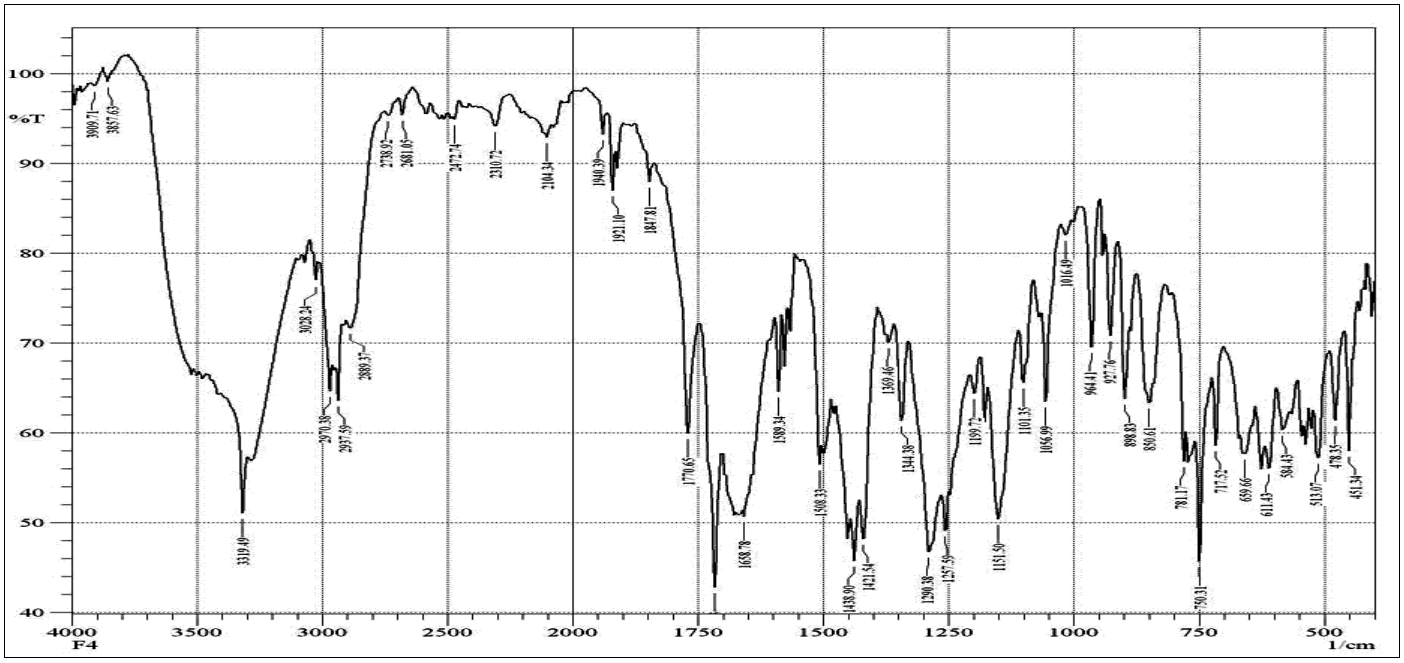

FIG. 7: FTIR SPECTRUM OF FORMULATION (F4)

CONCLUSION: The effervescent-based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel-forming polymer HPMC (K4M and E15M) and gas-generating agent sodium bicarbonate along with Magnesium stearate was essential to achieve *in vitro* buoyancy. FTIR study revealed no chemical interaction between drug and polymer.

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