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FORMULATION AND *IN-VITRO* CHARACTERIZATION OF FLOATING TABLET OF ENALAPRIL MALEATE

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ABSTRACT

The present study was aimed at developing an oral floating system for Enalapril maleate with the objective to enhance the oral bioavailability of the drug. As it is a prodrug, oxidizing agent $KMnO_4$ was used with distilled water and observed at 340 nm against a reagent blank, using PC Shimazdu UV Spectrophotometer. The obtained standard graph of drug was a straight line with coefficient correlation (R^2) = 9.9984. 12 formulations were prepared in 2 batches using varying concentration of hydrophilic swelling polymer HPMC K15 M and effervescent agent i.e. $NaHCO_3$. Having a light sensitive drug all the experimental work had been done in the dark light room. Among the different formulation B_1F_6 was considered as optimized formulation with a floating lag time of only 20 sec and floating time of more than 10 hour showed better floating behavior. It showed the release up to 60% of drug in 8 hr .The release of Enalapril maleate from all the formulations fitted to different release kinetic models, indicated that formulation B_1F_1 followed higuchi model and remaining all the formulation followed first order release kinetics. Among all, B_1F_6 showed maximum R^2 value i.e. 0.9789 which insured uniform release profile as compared to other formulations. This result was encouraging, because a longer gastric residence time of tablet could certainly enhance the low oral bioavailability of the drugs by avoiding the incomplete absorption due to narrow absorption window.

INTRODUCTION: The floating sustained release dosage forms [1-4] present most of the characteristics of hydrophilic matrices and are known as 'hydro dynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface.

The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents.

Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxy propyl methylcellulose. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy.

Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. Those drugs which acting locally in the stomach, primarily absorbed in the stomach or upper part of the small intestine, poorly soluble at the alkaline pH,

narrow window of absorption in the upper part of the small intestine, degraded in the colon ,having very less absorption in the colon are suitable for FDDS. Among the different applications of FDDS Recent study indicated that the administration of **Diltiazem** floating tablets twice a day may be more effective compared to normal tablets in controlling the B.B of hypertensive patients, **Modapar® HBS** containing L-Dopa and Benserazide, here the drug was absorbed over a period of 6-8 hours and maintained substantial plasma concentration for Parkinsonian patients. **Cytotech®** - containing Misoprostol, a synthetic prostaglandin –EL analogue, for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs (NSAIDS), **Fluorouracil** have been successfully evaluate in the patients with stomach neoplasm. HBS dosage form for **tacrin** provide better delivery tablet and reduced its GI side effects.

The aim of the present work is to Formulate and In-Vitro Evaluation of Gastro-retentive Floating Tablet of ACE-Inhibitor i.e. Enalapril Maleate[5-8] by Direct Compression Methods with the objective to enhance the oral Bioavailability of the drug. The drug have an oral bioavailability of just 40 to 60 %, seems to be due to the narrow absorption window in the upper part of small intestine, which demands the increment of Gastric Residence Time of the dosage form in stomach, from where drug will slowly release from the dosage form and completely get absorbed in the upper part of small intestine.

Any previous attempt for Gestroretentive Drug Delivery System of Enalapril maleate has not been reported before. As it is a light sensitive drug, it is stored in a dark condition. Enalapril maleate is a prodrug is an antihypertensive coming under the class of ACE inhibitors, is a off - white, crystalline powder. Freely soluble in methanol, (95%) soluble in ethanol, sparingly soluble in water, slightly soluble in semi polar organic solvents and practically, insoluble in non-polar organic solvents. e. g. Dichloromethane. Here Hydroxy propylmethyl cellulose (HPMC K-15M) [9] is used as polymer due to its direct compression and sustained release properties. Is an odorless, tasteless, white or creamy-white colored fibrous and granular powder. Acidity / Alkalinity - pH = 5.5 – 8.0 for 1% w/w aqueous solution, Tapped Density: 0.5 – 0.7 g/cm^3, Specific Gravity 1.26.

It is widely used in oral & topical pharmaceutical formulation. In oral product, HPMC is generally used as tablet binder, in film coating & as an extended release matrix tablets 2-5% w/w concentration is suitable as binder in either wet or dry granulation process. High viscosity grades may be used to retard the release of water-soluble drug from matrix. Sodium bicarbonate is used as the gas generating agent or floating agent in the present work. It is an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms.

Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available. It is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. Recently, sodium bicarbonate has been used as a gas-forming agent in alginate raft systems and in floating, controlled-release oral dosage forms of furosemide and cisapride. Tablet formulations containing sodium bicarbonate have been shown to increase the absorption of paracetamol and improve the stability of levothyroxine. Other excipient used are the lactose and magnesium stearate as the diluents and lubricant respectively.

Ravi Kumar *et al.*,[10] Designed and evaluated the oral floating matrix tablets of Aceclofenac by Melt granulation technique using polymers HPMC K15M, Ethyl cellulose, Bees wax, Cetyl alcohol, Glycerin monostearate, Sod. Bicarbonate. **R. Margret -chandira *et al.***, [11] reported about formulation and evaluation of Gasroretentive drug delivery system of Gastro-prokinetic Drug Itopride Hydrochloride. **J.A. Raval *et al.,*** [12] reported about Ranitidine Hydrochloride floating matrix tablets based on low density powder : effects of formulation on processing parameters on drug Release by direct compression techniques using polymers HPMC K4M, HPMC K100M, HPMC K15M, Sodium alginate, Psyllum, Sesbania gum and Gum acacia. Tablets were physically characterized and evaluated for in-vitro release characteristic for 8hrs.

Ziyaur Rahman *et al.,* [13] reported about the design and evaluation of bilayer floating tablets of Captopril using direct compression technology taking HPMC K-grade & effervescent mixture of Citric acid & Sod. Bicarbonate. They found approx. 95% drug release in 24 hours in-vitro, while the floating lag time was 10 min and the

tablet remain floatable throughout all studies and they got satisfactory results regarding physical appearance, drug content, and floatability or in-vitro dissolution pattern.

EXPERIMENTAL:

Materials and instruments used:

TABLE 1: SOURCES OF INGREDIENTS

INGREDIENT	SOURCE
Enalapril Maleate	Gift sample from Abbott pharmaceuticals Ltd, Baddi, (H.P).
HPMC K15M	Gift sample from Genovo Development services Ltd, R & D Center, Bangalore
Lactose	LOBA Chemie PVT, LTD , Mumbai
Sodium bicarbonate	Nice Chemicals, PVT, Ltd, Cochin
Magnesium stearate	Central Drug House, PVT, Ltd, Delhi
Talc	LOBA Chemical PVT, LTD , Mumbai
Distilled Water	TPC, Barpali
DM Water	TPC, Barpali

All the chemicals and reagents used were of analytical grade and also satisfying pharmacopoeias specifications.

TABLE 2: INSTRUMENTS USED

Analytical Digital Balance	Precisa 205ASCS, Rolex, India
Standard Sieve	Rolex. Ambala
Tablet Punch machine	Single Punch Hand Operated Rolex. India
Friability Tester	Thermonik, FT-20, Cambell electronics
Monsanto hardness tester	Rolex. Ambala
pH meter Apparatus	Unilab India
Stage Dissolution Apparatus	ELECTROLAB, Model:-TDT-08 L, USP
Double beam UV	SHIMADZU, Model: - UV-1800

Preformulation studies: Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development. The use of Preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product and at same time provides the basis for optimization of the drug product quality.The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage form.

Organoleptic properties: The color, odor, and taste of the drug were recorded using descriptive terminology. The results are given in **Table 5.**

Identification of drug by melting point test: Determination of melting point was done by filling of powder in a capillary tube up to 8mm height and then it was placed in a melting point apparatus.

Observation of λ_{max} of the drug by UV visible spectrophotometer: Accurately 10mg of the drug was weighted and it was transferred in a 10ml of volumetric flask and makes it up to 10ml with methanol. From this solution,1ml was withdrawn and again diluted to 10ml with methanol in an another volumetric flask and concentration in this stage was 100mcg/ml and the solution was examined in UV-visible spectrophotometer at the range of 190 to 1100nm.

Preparation of Standard Curve of Enalapril Maleate [14-17]: A 10mg of pure Enalapril Maleate was dissolved in 10ml of Distilled water to have conc. of 1mg/ml or 1000µg/ml. Different aliquots of standard solution (0.5, 1, 1.5, 2, 2.5) ml of 40µg/ml of pure Enalapril Maleate were transferred into a series of 10ml calibrated volumetric flasks by means of micropipette to give the conc. of (2, 4, 6, 8, 10) µg/ml and the total volume was adjusted to 3ml with water. To each flask was added accurately measured 1ml of 150µg/ml $KMnO_4$. The flasks were kept aside for 10 min with occasionally shaking before diluting to the mark with water. The absorbance was recorded after 5 min at 340 nm against a reagent blank, using PC Shimadzu UV Spectrophotometer. The standard curve of Enalapril Maleate was plotted between different concentration Vs absorbance. Results are given in **Table 6 and Fig. 1.**

Drug Polymer Compatibility study by FTIR Spectroscopy [18]: FTIR Study is one of the important analytical techniques to predict the presence of certain functional groups which are observed at a definite frequency. A peak-by-peak correlation is excellent evidence for identity. The drug-polymer interaction was studied by FTIR spectroscopy given in **fig. 6 & 7 and Table 15.**

Method of preparation: Floating matrix tablets of Enalapril maleate were prepared by direct compression technique by using ingredients i.e. HPMC K15M, Lactose monohydrate, Talc, Magnesium Stearate and Sodium bicarbonate.

Sodium bicarbonate was added as a gas generating agent, which was used to maintain the buoyancy (floating) of the tablets by producing carbon dioxide in the gastric environment. Drug and polymer (HPMC K-15 M) were mixed thoroughly and to it other excipients except Talc and Magnesium stearate were added and mixed by geometrical mixing. The mixture was passed through the sieve no 60. Finally Talc and Magnesium stearate were added with the mixture and punched in a single die punching machine. The details of composition are given in **Table 3 & 4.**

Evaluation Of Floating Tablet [19-29]:

1. **Floating behavior of the tablets:** The *in vitro* buoyancy was determined by the floating lag time (time period between placing the tablet in the medium and the floating time) method described by Rosa et al, 1994.Tabletes were placed in a 100 ml beaker containing 0.01 N HCl. The time required for the tablets to rise to the surface and float was taken as the floating lag time. The results are given in **Table 13 & 14**.

2. **Hardness study:** The tablet was placed between two anvils of hardness tester (Monsanto) and force (kg) was gradually increases in order to get exact reading. The reading at the marked scale was recorded for the pressure, which was required to break the tablets. Results shown in **Table 9, 10.**

3. **Friability:** Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again .The observed value should not be more than 1 %.The percentage friability was measured using the following formula. **Table 9, 10.**

$$\% F = \{1-(Wt/W)\} \times 100$$

Where, % F = friability in percentage, W = Initial weight of tablet, Wt = weight of tablets after revolution.

4. **Drug content:** Five tablets of each batch were taken and triturated. Powder equivalent to 100mg of drug was weighed and transferred to 100 ml volumetric flask and then 0.01N HCl was added and was shaken for 5 minutes and finally 0.01N HCl was added to make the volume up to 100ml and solution was then sonicated for 15 minutes and filtered through whatman filter paper. Finally a solution was diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 203nm using UV Visible spectrophotometer against 0.01N HCl blank. Results are given in **Table 11& 12.**

5. **Weight variation:** Twenty tablets were randomly selected from each batch and individually weighed using an electronic balance. The average weight and standard deviation of 20 tablets was calculated. Mean and SD were calculated shown in **Table 9 & 10.**

6. ***In vitro* Dissolution studies:** *In vitro* dissolution studies of all the formulations of floating tablets of Enalapril were carried out in 0.01 N HCl at 37 ± 0.5°C. The study was performed for 10 h and cumulative drug release was calculated at every one-hour time interval. It was observed that the different concentration of HPMC polymer affects the drug release pattern. The dissolution study was carried out under sink condition. *In vitro* dissolution studies of all the formulations are shown in **figure 2, 3, 4, 5 and Table No 15**.

7. **Mechanism of Drug Release:** To find out the mechanism of drug release from hydrophilic matrices, the dissolution data of floating tablet of each batch treated with different kinetic release equations. The released data were plotted according to Zero order, First order, Higuchi square root law and Hixson Crowell cube root method. The comparative coefficient correlation value is given in **table 16**.

TABLE 3: DIRECT COMPRESSION METHOD BATCH-1

INGREDIENT (mg per tablet)	Formulation					
	B_1F_1	B_1F_2	B_1F_3	B_1F_4	B_1F_5	B_1F_6
Enalapril Maleate	20	20	20	20	20	20
HPMC K 15 M	60	60	60	60	60	60
Sodium Bicarbonate	4	8	16	24	32	40
Lactose	83	79	71	63	55	47
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight of tablet (mg)	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**	**171.2**

TABLE 4: DIRECT COMPRESSION METHOD BATCH-2

INGREDIENT (mg per tablet)	Formulation					
	B2F1	B2F2	B2F3	B2F4	B2F5	B2F6
Enalapril Maleate	20	20	20	20	20	20
HPMC K 15 M	80	80	80	80	80	80
Sodium Bicarbonate	4	8	16	24	32	40
Lactose	63.2	59.2	51.2	43.2	35.2	27.2
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight of tablet (mg)	171.2	171.2	171.2	171.2	171.2	171.2

RESULTS AND DISCUSSION:

Organoleptic properties of drug: The color, odor, and taste of the drug were recorded using descriptive terminology. The results presented in **table 5** were found to be concordant with that mentioned in USP and 24-NF.

TABLE 5: ORGANOLEPTIC PROPERTIES OF THE DRUG:

PROPERTY	OBSERVATION
Color	white to off-white slightly yellowish crystalline power
Odour	Odorless
Taste	Characteristic

Melting point test: Melting point result was found to be 240°C, which complies with the standard value of I.P, BP and USP.

λ_{max} of the drug by UV visible spectrophotometer: The methanolic solution of drug was examined in UV-visible spectrophotometer at the range of 190 to 1100nm and the λ_{max} was found to be 287 nm which was comply with the standard value of I.P, BP and USP.

Standard Curve of Enalapril Maleate: The prepared standard curve of drug is a straight line with R^2 value 0.9984 was indicating that the drug follows Beer's law within the specified concentration range.

TABLE 6: STANDARD CURVE OF ENALAPRIL MALEATE

Sr. No.	Concentration (µg/ml)	Absorbance at λ_{max} 340 nm
1	0	0
2	2	0.067
3	4	0.127
4	6	0.190
5	8	0.241
6	10	0.310

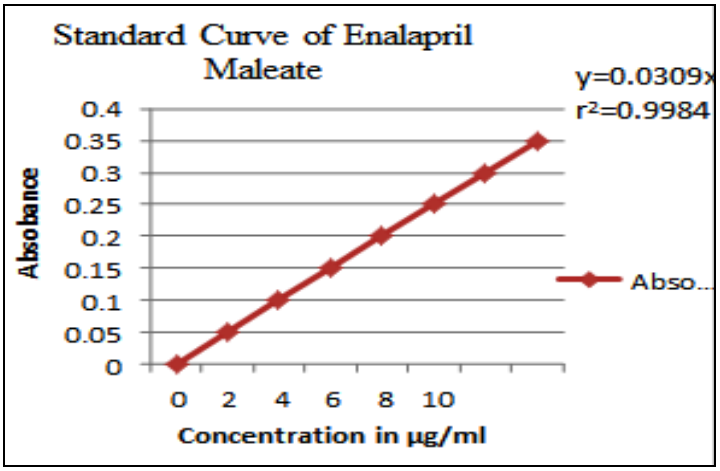

FIG. 1: STANDARD CURVE OF ENALAPRIL MALEATE

Evaluation of the Bulk Powder characterization parameters of Formulated Powder Blends: Formulation of proper powder blend is the key factor in the production of tablet dosage form involving floating extended release of drug from matrix type particle. Physical parameters such as specific surface area, shape, hardness, surface characteristics and size

can be significantly affect the rate of dissolution of drugs contained in a complex system. The formulated powder blends of different formulations were evaluated for angle of repose, tapped density, bulk density, Carr's index and Hausner ratio (**Table 7 & 8**). The results of angle of repose (<25) indicated good flow properties of the entire formulated blend. The compressibility index value were recorded, result in good to excellent flow properties.

Formulated powder blends density; porosity and hardness are often interrelated properties and are likely to influence compressibility, porosity, dissolution profile and properties of tablets made from it. The results of percentage porosity indicating that the packaging of the blend may range from close to lose packaging and also confirming that particle are not of greatly different sizes. All these results indicate that the formulated powder blend possessed satisfactory flow properties and compressibility.

TABLE 7: BATCH-1 BULK POWDER CHARACTERIZATION PARAMETERS

Formulation code	AOR in degree = $\tan^{-1}$ (h/r)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's index	Hausner Ratio
B1F1	15.1	0.57	0.71	19.0	1.24
B1F2	12.4	0.55	0.67	16.9	1.20
B1F3	10.2	0.55	0.70	19.9	1.27
B1F4	14.0	0.54	0.73	21.5	1.35
B1F5	17.7	0.53	0.67	20.8	1.25
B1F6	16.6	0.57	0.74	23.1	1.29

AOR= Angle of Repose, h=hight, r =radius, gm= gram, cm=centimeter

TABLE 8: BATCH-2 BULK POWDER CHARACTERIZATION PARAMETERS

Formulation code	AOR in degree = $\tan^{-1}$ (h/r)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's index	Hausner Ratio
B2F1	17.4	0.53	0.66	20.8	1.26
B2F2	16.8	0.57	0.74	22.1	1.29
B2F3	15.2	0.56	0.74	24.7	1.30
B2F4	18.7	0.57	0.73	22.8	1.32
B2F5	17.5	0.58	0.72	18.7	1.24
B2F6	18.3	0.55	0.71	19.4	1.27

AOR= Angle of Repose, h=hight, r =radius, gm= gram, cm=centimeter

Results of Post formulation Properties of Enalapril Maleate Tablets: The tablets of different formulations were evaluated for various parameters viz; thickness, diameter, hardness, friability, percentage weight variation (**Table 9 & 10**) and percentage drug content (**Table 11 & 12**). All the formulations showed uniform thickness and diameter. In a weight variation test, the pharmacopoeial limit for the percentage deviation for the tablets of more than 350mg is ±5%. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Drug content was found to be uniform among different batches of the tablets, and the percentage of the drug content was more than 96%. The hardness of all the formulation was between 4.0 to 5.5 kg/cm^2. The percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacopeial properties and complied with the in-house specifications for weight variation, drug content, hardness and friability.

TABLE 9: BATCH-1 POST FORMULATION PROPERTIES

Formulation code	% of Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)
B1F1	170 ± 2	5.3± 0.01	9.9±0.01	4.0± 0.01	0.28± 0.01
B1F2	170 ± 5	5.5± 0.01	9.9±0.02	5.0± 0.01	0.22± 0.01
B1F3	170 ± 4	5.3± 0.01	9.9±0.01	5.0± 0.01	0.18± 0.01
B1F4	170 ± 3	5.3± 0.01	9.9±0.02	5.0± 0.01	0.44± 0.01
B1F5	170 ± 2	5.4± 0.01	9.9±0.01	4.5± 0.01	0.38± 0.01
B1F6	170 ± 4	5.2± 0.01	9.8±0.02	5.0± 0.01	0.49± 0.01

Mg= milligram, mm= millimeter, kg=kilogram, cm=centimeter, %=percentage

TABLE 10: BATCH-2 POST FORMULATION PROPERTIES

Formulation code	% of Weight Variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)
B2F1	**170 ± 3**	**5.2± 0.01**	**9.9±0.02**	**4.5± 0.01**	**0.23± 0.01**
B2F2	**170 ± 4**	**5.4± 0.01**	**9.9±0.03**	**4.0± 0.01**	**0.26± 0.01**
B2F3	**170 ± 5**	**5.5± 0.01**	**9.9±0.01**	**5.5± 0.01**	**0.19± 0.01**
B2F4	**170 ± 2**	**5.3± 0.01**	**9.9±0.03**	**5.0± 0.01**	**0.42± 0.01**
B2F5	**170 ± 3**	**5.2± 0.01**	**9.9±0.02**	**4.0± 0.01**	**0.36± 0.01**
B2F6	**170 ± 2**	**5.3± 0.01**	**9.8±0.01**	**5.5± 0.01**	**0.40± 0.01**

Mg= milligram, mm= millimeter, kg= kilogram, cm=centimeter, %= percentage

TABLE 11: BATCH-1 PERCENTAGE OF DRUG CONTENT

Formulation code	Percentage of Drug content
B1F1	98.6
B1F2	96.1
B1F3	97.0
B1F4	96.1
B1F5	96.1
B1F6	95.6

TABLE 12: BATCH-2 PERCENTAGE OF DRUG CONTENT

Formulation code	Percentage of Drug content
B2F1	95.6
B2F2	96.3
B2F3	97.2
B2F4	97.6
B2F5	95.7
B2F6	97.5

3.7 In vitro Buoyancy study: From the results of floating behavior studies, (**Table 13 & 14**) it was found that as the concentration of effervescent mixture increase, the floating lag time, floating duration and matrix integrity decreased and vice versa. A reverse trend was observed on increasing the polymer concentration. The initial batches were prepared without sodium bicarbonate did not show any sign of floating. Therefore, sodium bicarbonate was used as a gas-generating agent in order to float the tablet. The sodium bicarbonate induces CO_2 generation in the presence of dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/ml, and the tablet becomes buoyant. To study the effect of sodium bicarbonate concentration on floating lag time, two to three tablets from each batches are selected. It was found that as the amount of sodium bicarbonate increases, the floating lag time decreases.

Thus, sodium bicarbonate was essential to achieve optimum *in vitro* buoyancy (i.e., floating lag time of 4 to 5 minutes and floating duration of 12 hours). Further increase in concentration of sodium bicarbonate does not show any significant effect on floating behavior. Moreover, the increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby to rapid drug release.

TABLE 13: BATCH-1 EFFECT OF SODIUM BICARBONATE ON FLOATING EFFECT OF TABLET

Formulation code	Amount of Sodium bicarbonate (mg)	Buoyancy Lag Time (min)	Total Floating time (hrs)
B1F1	4	Did not float	Did not float
B1F2	8	Did not float	>4
B1F3	16	5.20	>6
B1F4	24	3.28	>8
B1F5	32	1.12	>10
B1F6	40	0.20	>10

Mg=milligram, min=minutes, hrs=hour,>=greater than < = smaller than

TABLE 14: BATCH-2 EFFECT OF SODIUM BICARBONATE ON FLOATING EFFECT OF TABLET

Formulation code	Amount of Sodium bicarbonate (mg)	Buoyancy Lag Time (min)	Total Floating time (hrs)
B2F1	4	Did not float	Did not float
B2F2	8	Did not float	>4
B2F3	16	4.58	>6
B2F4	24	3.10	>8
B2F5	32	1.04	>10
B2F6	40	0.16	>10

Mg=milligram, min=minutes, hrs=hour,>=greater than. < = smaller than

***In-vitro* Dissolution Studies:** Based upon Floating lag time and total floating time formulation F3 to F6 of each batches were selected for dissolution study for 8 hour. The results obtained from *in vitro* dissolution studies of all the formulations were shown in **fig 2, 3, 4 & 5**. *In vitro* dissolution studies for all the formulations showed slow release of drug for more than eight hours. When the floating tablets were exposed to dissolution medium, the medium penetrated into the free spaces between macromolecular chains of the polymer.

After solvation of the polymer chain, the dimension of the polymer molecule is increased due to the polymer relaxation by stress of the penetrated solvent. This led to swelling which is characterized by the formation of a gel like network surrounding the tablet. HPMC is a hydrophilic polymer that forms a surface barrier around the matrix tablet. It can be noted that the increase in the concentration of $NaHCO_3$ in Batch 1 and in Batch 2 doesn't have any significant effect of the release behavior of the drug from the dosage form.

The main difference between batch 1 an batch 2 is the concentration of HPMC K 15M used as the sustained release polymer. From **Table 15** it can be noted that the formulations B1F3, B1F4, B1F5, B1F6 shows 56.3214, 59.3215, 61.9386, 59.9031 % and formulations B2F3, B2F4, B2F5, B2F6 shows 60.3393, 58.5945, 33.8772 and 44.4911% drug release respectively after 8 hour, which indicates no significant difference due to increase in polymer concentration.

From **Table 15** and **Fig2** it can be noted that amongs the different formulations, B1F6 shows near 60% of drug release in a consistent manner. The release profile of drug from all the formulations fitted to different release kinetic models given in **Table 16** and **Fig. 2, 3, 4 & 5**, which clearly indicates that formulation B1F1 follows higuchi model and remaining all the formulation follows first order release kinetics. Among the all formulations B1F6 shows maximum R^2 value i.e. 0.9789, which indicates better release profile as compared to other formulations.

TABLE 15: CUMULATIVE PERCENTAGE DRUG RELEASE FOR 8 HOUR

Time (hr)	DB1 F 3	DB1F4	DB1 F5	DB1F6	DB2F3	DB2F4	DB2F5	DB2F6
1	1.59935	2.18094	1.7447	13.0856	23.2633	2.90792	7.2697	7.2697
2	20.7915	17.0113	22.2456	15.2666	18.1745	4.07108	1.8901	2.0355
3	19.9192	24.2811	24.2811	22.5363	24.2811	18.9015	2.3263	9.1599
4	34.1680	33.0048	29.5153	34.168	33.0048	24.8627	11.7771	19.3376
5	39.8384	39.8384	39.8384	42.8918	42.4556	31.9871	16.4297	24.1357
6	45.3634	45.3635	48.7076	53.0695	51.9063	48.7076	24.4265	29.5153
7	46.0904	51.4701	53.0695	57.7221	57.7221	53.6511	29.37	34.3134
8	56.3214	59.3215	61.9386	59.9031	60.3393	58.5945	33.8772	44.4911

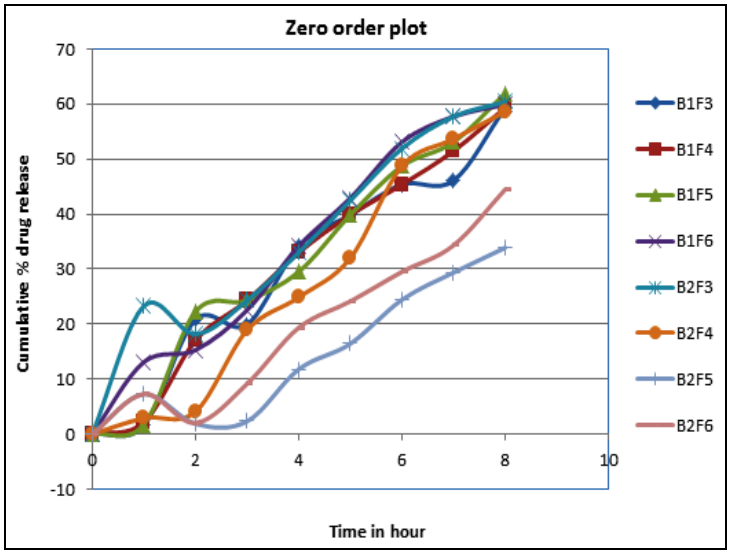

FIG. 2: CUMULATIVE PERCENTAGE DRUG RELEASE VS TIME IN HOUR

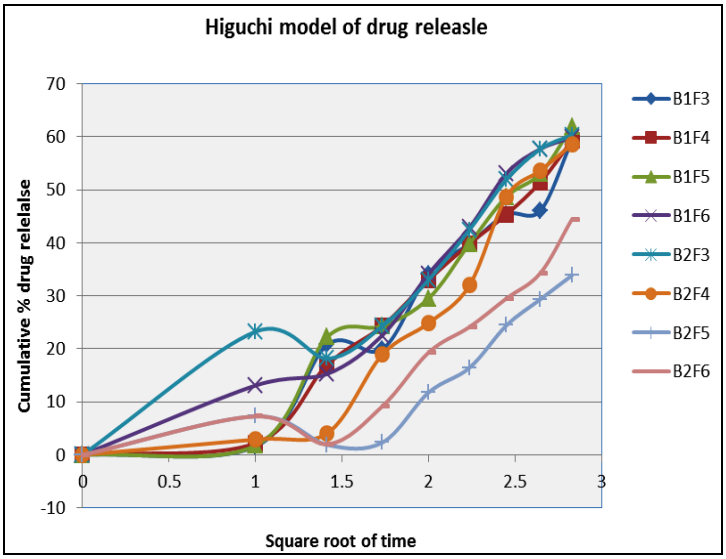

FIG. 3: CUMULATIVE% DRUG RELEASE VS. SQUARE ROOT OF TIME

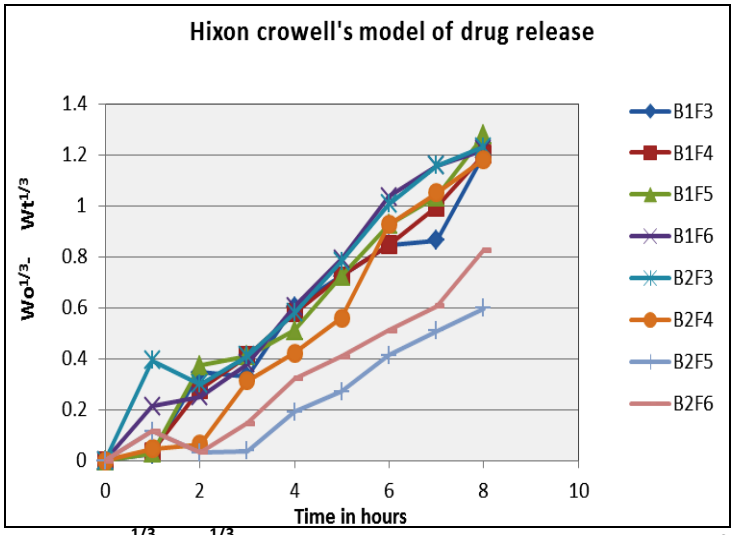

FIG. 4: $Wo^{1/3}$- $Wt^{1/3}$ VS TIME IN HOURS. Wo = initial mass of tablet, Wt = mass of the tablet after time "t"

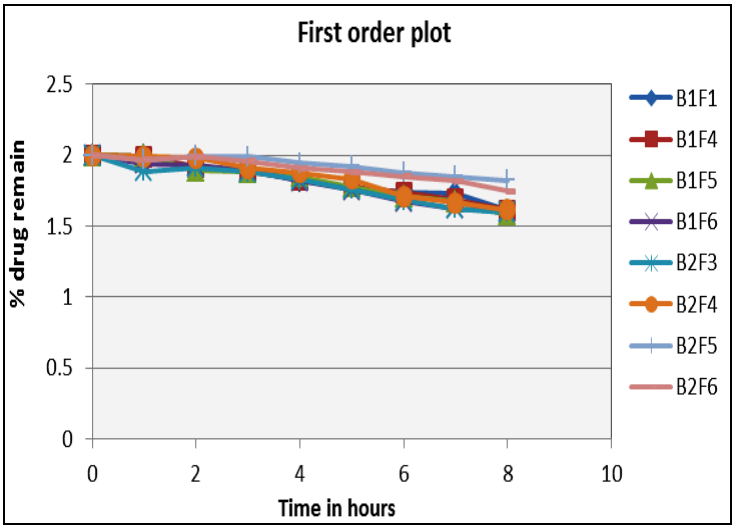

FIG. 5: LOG % DRUG REMAIN VS TIME IN HOURS

TABLE 16: COMPARISON OF R^2 (COEFFICIENT OF CORRELATION) VALUES OF DIFFERENT RELEASE KINETICS

Batch	Formulation	R^2 Value For Zero Order	R^2 Value For First Order	R^2 Value For Higuchi Kinetics	R^2 Value For Hixson Crowell Kinetics	Release mechanism
1	**B1F3**	0.9318	0.9618	0.9045	0.9653	Predominantly Hixson Crowell Kinetics
	B1F4	0.9318	0.9679	0.8583	0.9653	Predominantly First order
	B1F5	0.9443	0.975	0.8586	0.9267	Predominantly First order
	B1F6	0.9628	0.9789	0.886	0.9434	Predominantly First Order
2	**B2F3**	0.9451	0.9557	0.9045	0.9431	Predominantly First Order
	B2F4	0.8834	0.9497	0.7445	0.8529	Predominantly First Order
	B2F5	0.9242	0.946	0.8222	0.9042	Predominantly First Order
	B2F6	0.8755	0.9308	0.7317	0.8519	Predominantly First Order

Drug Polymer Compatibility Study by FTIR:

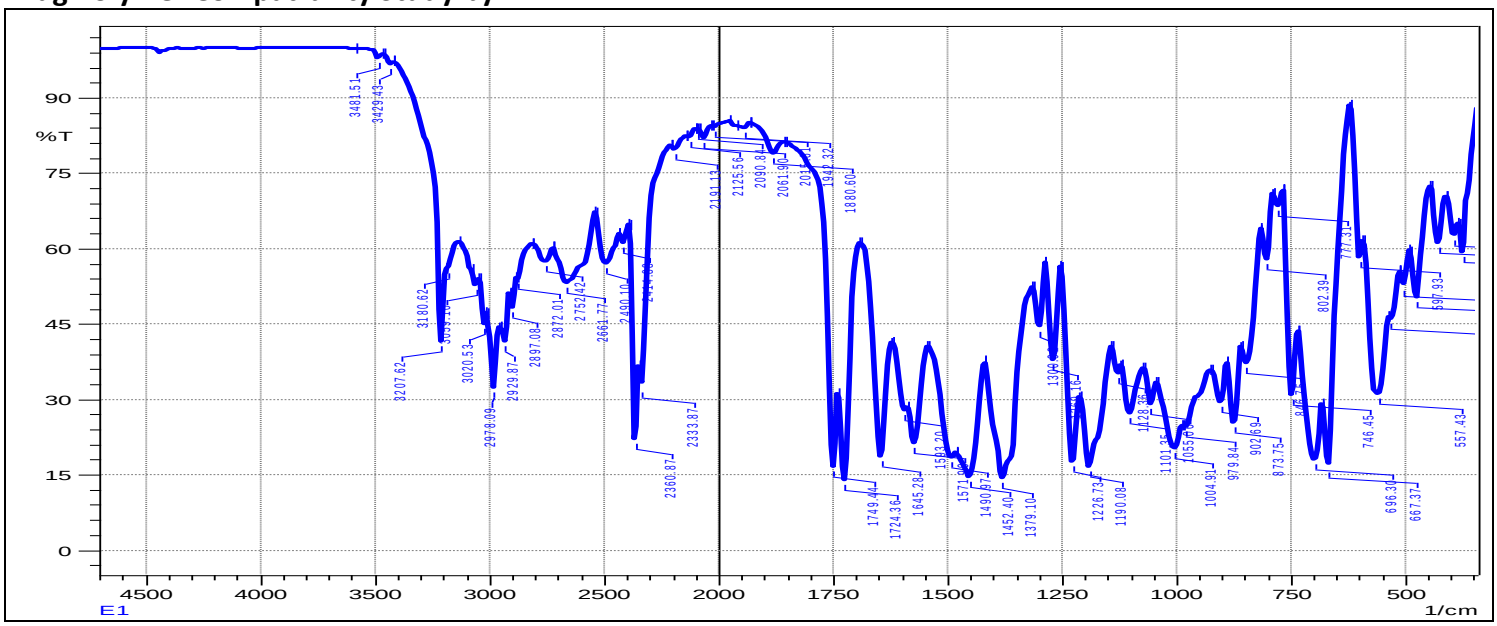

FIG. 6: FTIR SPECTRA OF DRUG

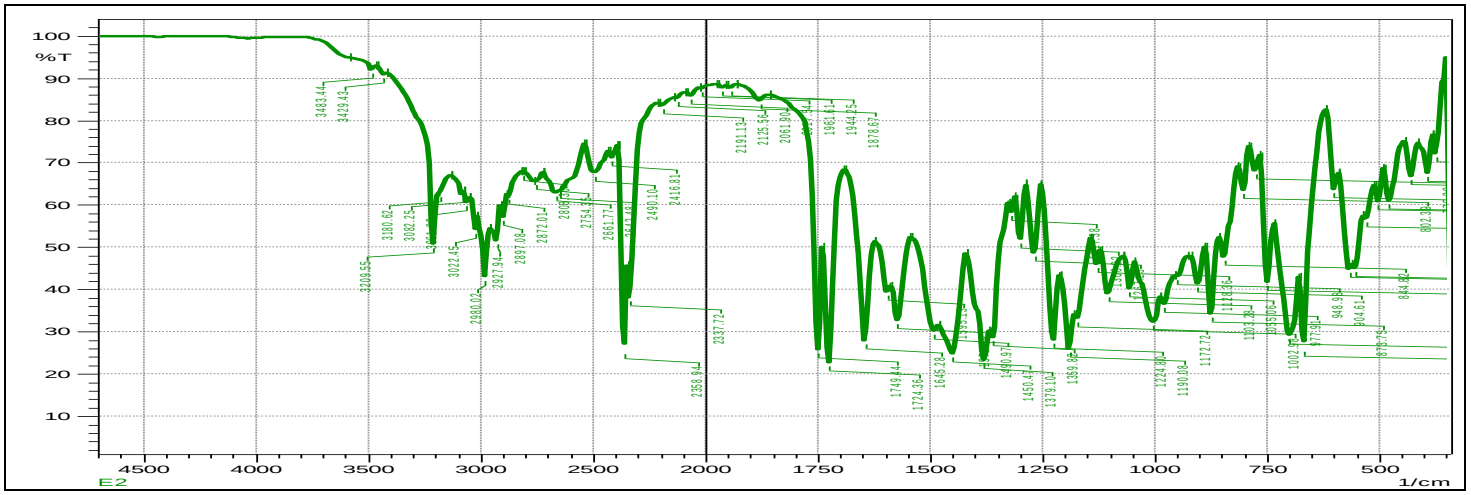

FIG. 7: FTIR SPECTRA OF DRUG AND POLYMER MIXTURE

From the above spectra the absorption shown by major functional groups of drug and polymer are tabulated below:

TABLE 17: FTIR ABSORPTION SPECTRA OF DIFFERENT FUNCTIONAL GROUPS OF DRUG AND DRUG POLYMER MIXTURE

Functional group	Absorption range (cm-1)	Absorption range of pure drug	Absorption range of Drug polymer mixture	Observation
-NH	1570-1515	1571.99	1571.99	Functional group present in both drug and drug polymer mixture
-C=O	1540-1870	1724.36	1724.36	Functional group present in both drug and drug polymer mixture
-Et OOC	1750-1735	1749.44	1749.44	Functional group present in both drug and drug polymer mixture
C_6H_6	1400-1500	1490.97	1490.97	Functional group present in both drug and drug polymer mixture
-COOH	3300-2500	2978.09	2980.02	Functional group present in both drug and drug polymer mixture
C_4H_8N	3500-3250	3429.43	3429.43	Functional group present in both drug and drug polymer mixture

FTIR Spectra of Drug (Enalapril Maleate) and Drug Polymer (HPMC) mixture were shown in table 15 & figures 6 & 7 reveled that there was no significant interaction between drug and polymer.

CONCLUSION: From the results and inference we can certainly say that floating type gastro retentive drug delivery system holds a lot of potential for drug having limited oral bioavailability due to having a narrow absorption window in the upper part of small intestine. We can certainly explore this drug delivery which may lead to improved bioavailability and ensured therapy with many existing drugs. It is the responsibility of future scientists working in this area to effectively use the potential of this drug delivery system for the benefit of mankind.

FUTURE SCOPE: Various studies have not been completed which may be taken off in future study

- Further improvement of formulation development.
- Pharmacokinetic study.
- *In vivo* study in animals
- Study on human subjects

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