FORMULATION AND EVALUATION OF HERBAL EFFERVESCENT FLOATING TABLET USING AEGLE MARMELOS FRUIT EXTRACT

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Abstract:

Background: Floating tablets prolong the gastric residence time of drugs, improves bioavailability, and facilitate local drug delivery to the stomach. With this objective, floating tablets containing extract of *Aegle marmelos* fruit as active ingredient was prepared for the treatment of peptic ulcer**.**

Material and method: Floating tablets of *Aegle marmelos* were prepared by direct compression method using sodium bicarbonate as effervescent agent, HPMC K4M and HPMC E15 as polymers, Magnesium stearate, Talc, Citric acid and Lactose. The formulations were evaluated for various physical parameters, floating lag time, *in-vitro* drug release, buoyancy time.

Result: The diameter of all formulations was in range 10-11 mm, thickness was in the range 4.02-4.086 mm. The hardness ranged from 3.1-3.3 kg/cm^2, All formulations passed the USP requirements for friability and uniformity of weight. The buoyancy time of all tablet formulations was less than 5min and tablet remained in floating condition throughout the study.

Conclusion: The optimized formulation was found to be F8 batch which released 98.13% of drug in 8hr *in vitro*, while the floating lag time was 35 seconds.

Keywords: *Aegle marmelos*, floating tablet, peptic ulcer, floating lag time, HPMC K4M, HPMC E15.

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INTRODUCTION:

According to World Health Organization, about 80% of the world population maintain their primary health care by using herbal medicine. Nowadays herbal drugs have gain wide spread acceptability. Floating drug delivery is a type of controlled drug delivery system which is capable of controlling the rate of drug delivery, prolong the duration of therapeutic activity and target the delivery of the drug to a specific site. Floating drug delivery system of tablet have bulk density less than gastric fluid and so remain buoyant in the stomach where the drug is release slowly in the upper GIT for local and systemic effect without affecting the gastric emptying rate for a prolonged period. In the effervescent tablet there is a use of swellable polymers and effervescent components which upon arrival in the stomach, carbon dioxide is released and entrapped within polymer causing the formulation to float in the stomach. Floating tablets prolong the gastric residence time of drugs, improve bioavailability, and facilitate local drug delivery to the stomach. Ulcer results due to unbalance between formation of gastric acid and maintenance of the protective mucosal barrier that depends on secretion of bicarbonate, prostaglandins and mucosal growth factors. Gastric ulcers are caused due to insufficient mucosal protection, whereas duodenal ulcers are caused due to excessive acid secretion. Helicobacter pylori infection is also responsible for gastric ulcers, in which bacteria disrupt the mucosal protective barrier which results in acid damage to stomach layer and inflammatory response. Literature review revealed that fruits of *Aegle marmelos* plant has great healing properties on account of its mucilage, which form a protective coating on the stomach mucosa and thus helps in the healing of ulcers. The ripe fruit pulp of *A. marmelos* shows gastrointestinal cytoprotective activity in Aspirin induced, cold restraint stress induced and cerebellar lesion induced ulcer through the release of serotonin from enterochromaffin cells. Therefore, in the present study the methanolic extraction of *A. Marmelos* is used in the preparation of antiulcer floating tablets[1-4].

Fig. 1: Bael Extract

Materials and Methods:

Materials:

The *Aegle marmelos* fruit powder were purchased from IYUSH HERBAL AYURVEDA. HPMC K4M and HPMC E15 was provided by CHEMDYES CORPORATION, Gujrat. Sodium bicarbonate was purchased from SOURAV SCIENTIFIC, Pune. Magnesium stearate was purchased from Pallav Chemicals and solvent Pvt. Ltd. Talc and Citric acid was purchased from THOMAS BAKER (chemicals) Pvt. Ltd, Mumbai. Lactose was gift sample from CHEMDYES CORPORATION, Gujrat, India. All chemicals used were of analytical and pharmaceutical grade.

Methods:

Extraction of *Aegle marmelos* fruits powder:

Take the sufficient quantity of *Aegle marmelos* fruit then cut it. Dry the fruits, after that fruits are powdered. Then the process of solvent extraction takes place with the 250ml ethanol in round bottom flask, which is attached to a soxhlet extractor and condenser. The crushed plant material is loaded into the thimble, which is placed inside the soxhlet extractor. The side arm is lagged with glass wool. The solvent is heated used in the isomantle and will begin to evaporate, moving through the apparatus to the condenser. The condensate then drips into the reservoir containing the thimble. Once the level of solvent reaches to the siphon it pours back into the flask and the cycle begins again. The process

should run for a total of 16 hours. Once the process has finished, the ethanol should be evaporated using a rotary evaporator, leaving a small yield of extracted plant material in the glass bottom flask[2].

Methodolody:

Analytical method development:

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ml drug was prepared in 0.1N HCL UV spectrum was taken by using UV spectrophotometer. The solution was scanned in the range of 200-400 nm.

b) Preparation calibration curve:

10mg *A. marmelos* fruit extract was dissolved in 10ml of 0.1N HCL(stock solution1) from stock solution1 1ml of solution was taken and made up with 10ml of 0. 1N HCL (100µg/ml). From this 1ml was taken and made up with 10 ml of 0. 1N HCL (10µg/ml). The above solution was subsequently diluted with 0. 1N HCL to obtain the series of dilutions containing 2, 4, 6, 8, 10 µg /ml of per ml of solution. The absorbance of above dilutions was measured at 236 nm by using the UV-Spectrophotometer taking 0. 1N HCL as blank. Then a graph was plotted by taking the concentration on X-Axis and absorbance on Y-Axis which gives a straight-line linearity of standard curve was assessed from the square of the correlation coefficient (R^2) which determined by the least-square linear regression analysis.

Drug - Excipient compatibility studies:

Fourier- Transform Infrared Spectroscopy (FT-IR):

The compatibility between the pure drug and the excipients was detected by the FT-IR spectra obtained on Bruker FT-IR Germany (Alpha T). The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-1}.

Pre-formulation parameters:

Preformulation is defined as the phase of research and development in which preformulation studies characterize physical and chemical properties of a drug molecule in order to develope safe, effective and stable dosage form[8].

Flow properties of powder (before compression) are characterized in the terms of Angle of repose, Carr's index and Hausner's ratio. Then for determination of:

Bulk density:

Bulk density of powder is a ratio of the mass of powder sample to its volume.

Bulk density = Mass/Bulk volume

Tapped density:

Tapped density of powder is a ratio of the mass of powder sample to its volume occupied by the powder after it has been tapped for the definite period of time.

Tapped density = Mass/Volume

Angle of repose:

The powder are poured through the walls of the funnel, which was fixed at position such that its lower tip was at height of exactly 2 cm above the surface of the graph paper. The powder were poured till the time when the lower tip of the channel. The formula for angle of repose is as below:

$\Theta = \tan^{-1}(h/r)$

Where,

Θ = Angle of repose

h = Height of the pile

r = Average radius of the base of piles

Carr's index:

Cars index determine the compressibility of a powder which is based on tapped density and bulk density. The formula for carr's index is as below:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Bulk density}} \times 100$$

Hausner's ratio:

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

Lower Hausner's ratio Better flow ability

Higher Hausner's ratio Poor flow ability.

Formulation of floating tablet of *A. marmelos* by direct compression method:

Floating tablets of *Aegle marmelos* were prepared by direct compression method using Sodium bicarbonate as a effervescent agent. HPMC K4M and HPMC E15 were used as a rate controlling polymers. Magnesium stearate were used as a lubricant, talc as a glidant and citric acid as a sequestering agent. Final weight was adjusted by using lactose as a filler/ binder. The concentration of above ingredients were taken as shown in Table No.1. All the ingredients were weighed accurately. The drug was mixed with the release rate retarding polymers and the mix was blended for 20 minutes to have uniform distribution of drug in the formulation. The blend was lubricated with magnesium stearate and talc and compressed using 6 station compression machine. The tablet weighed for compression was adjusted to 250 mg[8].

Table no.1. Formulation of effervescent floating tablets of *Aegle marmelos* fruit extract

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
***A.Marmelos* fruit extract**	75	75	75	75	75	75	75	75	75
HPMC K4M	25	31.25	37.75	-	-	-	25	31.25	37.75
HPMC E15	-	-	-	37.75	50	62.5	37.75	50	62.5
Sodium bicarbonate	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Citric acid	20.75	20.75	20.75	20.75	20.75	20.75	20.75	20.75	5
Lactose	61.75	55.5	49	49	36.75	24.25	24.25	5.5	2.5
Total	250	250	250	250	250	250	250	250	250

Evaluation of post-compression parameters of prepared tablets:

1) Diameter and Thickness:

The diameter and thickness of the tablets was determined by using Vernier caliper. The thickness of tablet is depends upon the diameter of the die. Five tablets were selected at random from each batch and average value were calculated.

2) Hardness test:

Hardness of the five tablets was determined using the Monsanto hardness tester and the average values were calculated.

3) Friability:

The friability of the tablets carried out in a Roche friabilator. Friability done with the 20 tablets adjust the time at 4 min and speed at 25 rpm.

$$\text{Friability (\%)} = \frac{W_1 - W_2}{W_1} \times 100$$

Where, W_1 = Initial Weight of Tablets

W_2 = Final Weight of Tablets

4) Weight variation test:

As per Indian pharmacopoeia, weight variation can be done by using 20 tablets and their weight was determined individually and correctly on a digital weighing balance the average weights of tablet was determined from the collective weight.

5) Content uniformity:

Percentage drug content of herbal floating tablets develop to ensure content consistency of active drug substance.

6) *In-vitro* disintegration time:

In-vitro disintegration test was carried out with the 6 tablet using 0.1N HCL at 37ºC ± 2°C was used as disintegration media and the time in a second taken for a complete disintegration of the tablet with no palatable mass remaining in the apparatus measuring in the seconds.

7) Determination of swelling index:

The drug release from any tablet depends upon percentage of intake of medium, the medium used as 0.1 N HCl. The medium of temperature was maintained at 37 ± 0.5ºC throughout the study. The swelling index was determined by the following equation:

$$\text{Swelling index} = (W_t - W_0) \times 100/W_0$$

Where,

W_0 = Initial weight of tablet

W_t = Weight of the tablet at time

8) Floating lag time (Buoyancy time):

The time intervals between the tablets took to emerge on the surface of 0.1 N HCl (floating lag time) and the time the tablets constantly float on the surface of 0.1 N HCl (duration of floating) were evaluated in 100 ml beaker.

9) *Invitro* drug release study:

The release rate of herbal floating tablet of *Aegle marmelos* fruit extract was determined as per United State Pharmacopoeia (USP) using dissolution testing apparatus 2 (Paddle method). The dissolution test was performed by using 900 ml of 0.1 N HCl (pH=1.2), at 37 ± 0.5ºC at 50 rpm. 10 ml samples were drawn with every one hour upto a period of 20-24 hrs. the samples were diluted suitably and filtered. The required dilutions were made with and the solution was analyzed for the drug content by using UV detector. From this % drug release was calculated and this was plotted against function of to the pattern of drug release[13].

RESULT AND DISCUSSION:

1) Calibration curve:

Graph of *A. marmelos* fruit extract was taken in 0.1N HCL (pH 1.2). Standard graph of *A. marmelos* fruit extract was plotted as per the procedure in experimental method and its linearity is shown in Table No.2 and Fig no.2. The standard graph of *A. marmelos* fruit extract show good linearity with R^2 of 0.99992, which indicates that it obeys "Beer-Lamberts" law.

Table no.2. Observation of graph of *A. marmelos* fruit extract in 0.1N HCl

Conc (µg/mL)	Absorbance
2	0.112
4	0.214
6	0.313
8	0.418
10	0.517

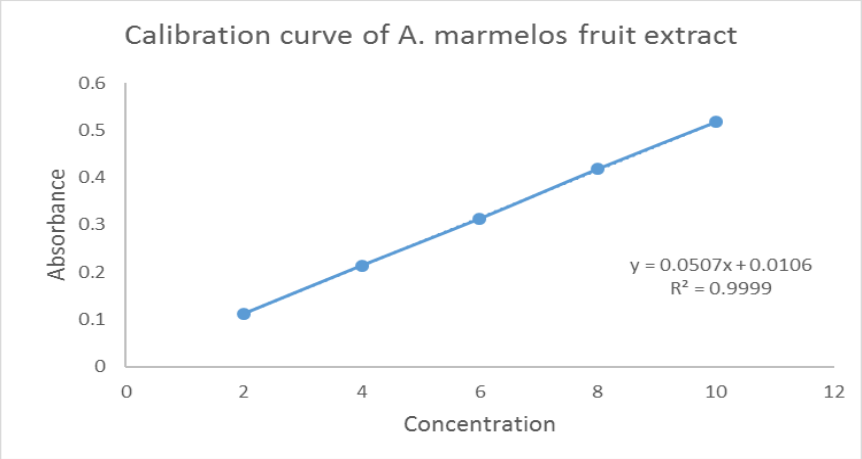

Fig no.2. Calibration curve of *A. marmelos* fruit extract in 0.1N HCL

2) FT-IR:

There was no disappearance of any characteristics peak in the FT-IR spectrum of drug and the polymers used. This indicates that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

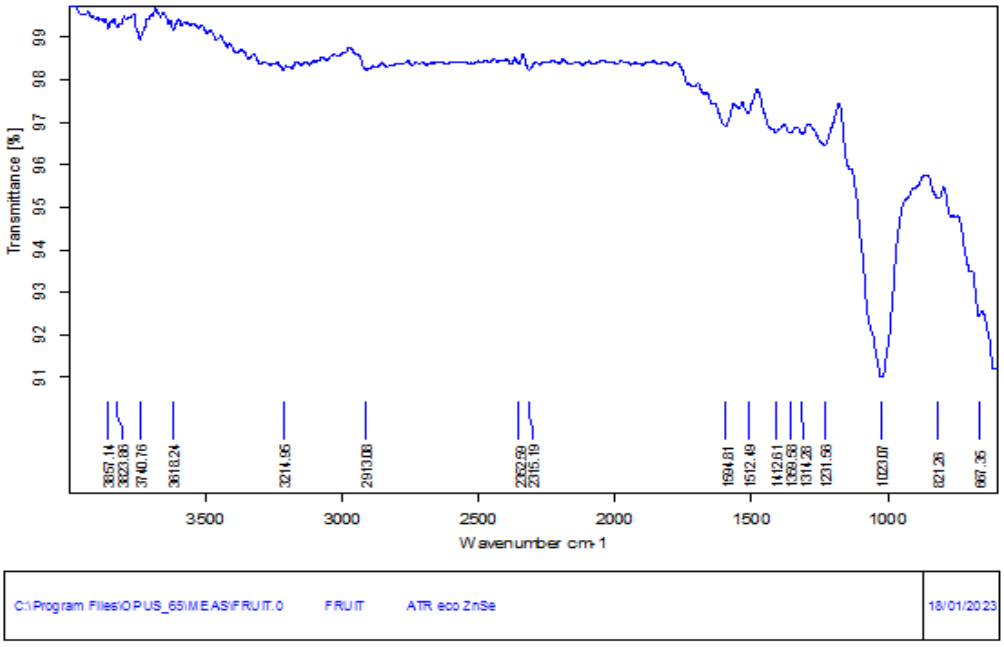

Fig.no.3. FT-IR *Aegle marmelos* fruit extract

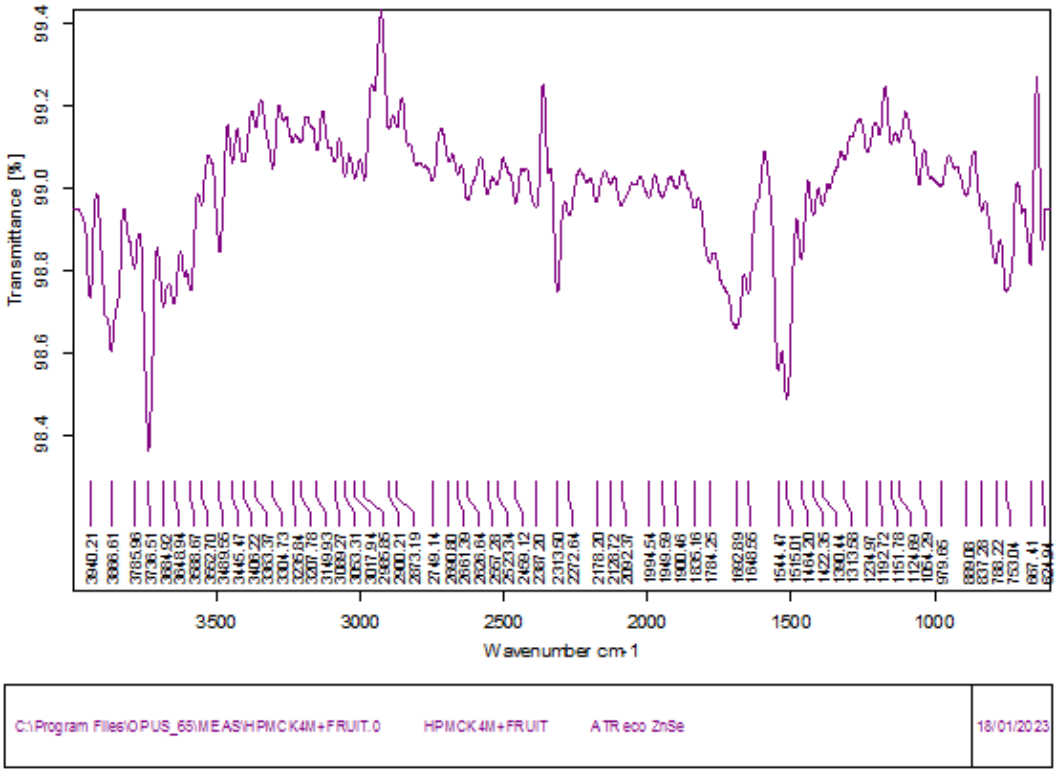

Fig.no.4. FT-IR of *A. marmelos* fruit + HPMC K4M

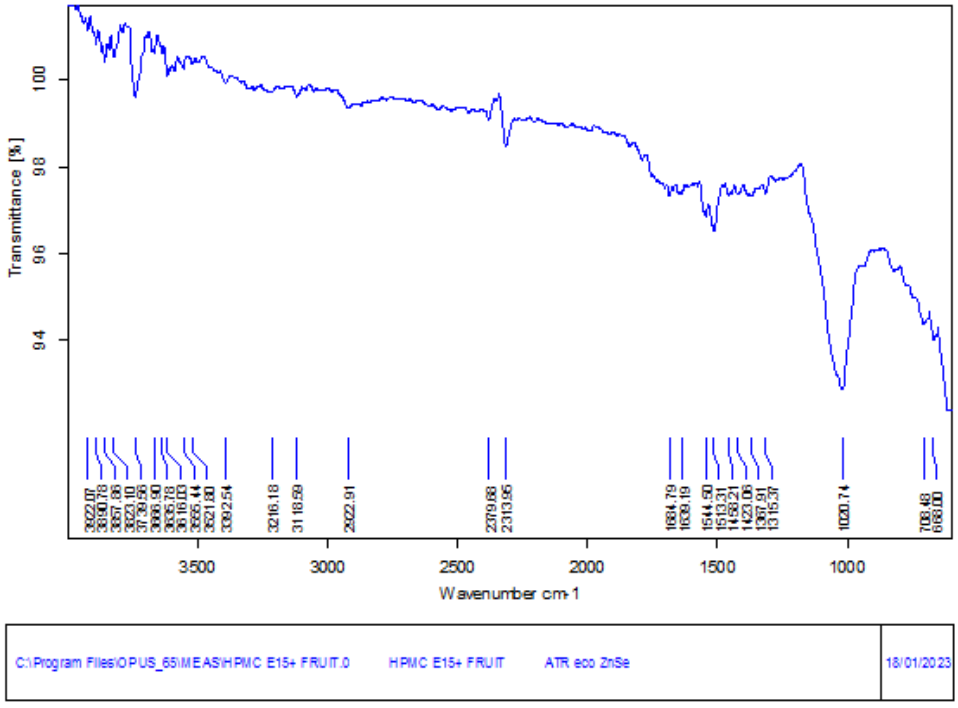

Fig.no.5. FT-IR of *A. marmelos* fruit + HPMC E15

3) Preformulation parameters:

From the above result of pre-compression parameter of tablet it was observed that the bulk density ranged between 0.54 to 0.68 g/ml and tapped density ranged between 0.68 to 0.83 g/ml, which make them floatable in the gastric fluid. The other micromeritic properties such as Carr's index, Hausner's ratio revealed no significant differences. Angle of repose was obtained between 34.59 to 38.66 indicating good flow properties. Hardness, friability, weight variation, thickness, disintegration time of tablet formulation were within acceptable limits and the drug content in all the batches of *A. marmelos* fruit extract ensured that the uniformity of the drug content in the tablets.

Table no.3. Evaluation of mixed blend of drug and excipients

Batches	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (º)
F1	0.6	0.75	20	1.25	38.66
F2	0.6	0.75	20	1.25	34.59
F3	0.68	0.83	18.07	1.22	37.04
F4	0.62	0.75	17.33	1.2	36.02
F5	0.58	0.68	14.70	1.17	38.66
F6	0.58	0.68	14.70	1.17	36.12
F7	0.63	0.75	16	1.19	35.15
F8	0.58	0.75	22.66	1.29	35.63
F9	0.54	0.68	20.59	1.26	35.53

4) Evaluation of post-compression parameters of prepared tablets:

Weight variation data of the tablets shows no significant difference in the weight of individual tablet from the average value. The diameter of all formulations was in range 10-11 mm, thickness was in the range 4.02-4.086 mm. The hardness ranged from 3.1-3.3 kg/cm^2, All formulations passed the USP requirements for friability and uniformity of weight. *In vitro* disintegration was found in the range 3.30-5 min, Swelling index was found in the range 29.29-38.23%. The buoyancy time of all tablet formulations was less than 5min and tablet remained in floating condition throughout the study.

Table no.4. Evaluation of Herbal Floating Tablet of *Aegle Marmelos* Fruit Extract

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	*Invitro* Disintegration time (min)	Friability (%)	Weight variation	Swelling index(%)	Floating lag time	Total floating time (Hrs)
F1	3.2 ± 0.098	4.02 ± 0.12	3.30 ± 0.577	0.7 ± 0.01	248 ± 0.012	32.23 ± 0.12	2.25 min	12
F2	3.22 ± 0.25	4.04 ± 0.57	3.50 ± 0.521	0.9 ± 0.05	250 ± 0.01	29.29 ± 0.13	2.36 min	10
F3	3.23 ± 0.09	4.02 ± 0.12	4 ± 1.003	0.5 ± 0.25	255 ± 0.053	30.09 ± 0.15	2.14 min	10
F4	3.18 ±0.144	4.08 ± 1.00	4.20 ± 0.09	0.7 ± 0.01	248 ± 0.012	32.29 ± 0.13	2.29 min	12
F5	3.3 ± 0.15	4.02 ± 0.57	4.30 ± 0.098	0.57 ± 0.25	251 ± 0.001	31.52 ± 0.13	2.21 min	11
F6	3.35 ± 0.13	4.03 ± 0.31	5 ± 1.523	0.55 ± 0.25	250 ±0.01	33.68 ± 0.18	2.06 min	12
F7	3.33 ± 0.17	4.04 ± 0.12	5 ± 1.523	0.73 ± 0.13	257 ± 0.058	31.52 ± 0.13	2.21 min	11
F8	3.25 ± 0.18	4.05 ± 0.21	4.45 ± 0.51	0.7 ± 0.01	250 ± 0.01	38.23 ± 0.12	35 sec	12
F9	3.37 ± 0.09	4.08 ± 1.00	4.49 ± 0.68	0.79 ± 0.57	252 ± 0.051	35.96 ± 0.19	43 sec	12

Floating lag time:

Fig.no.6. At initial time

Fig.no.7. After 20 sec

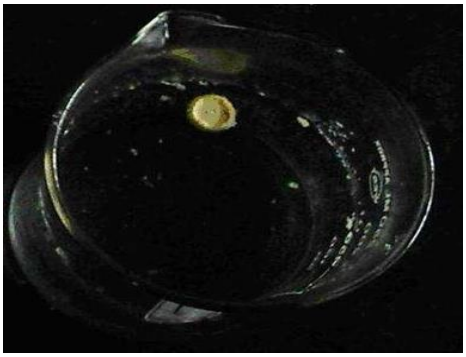

Fig.no.8. After 35 sec

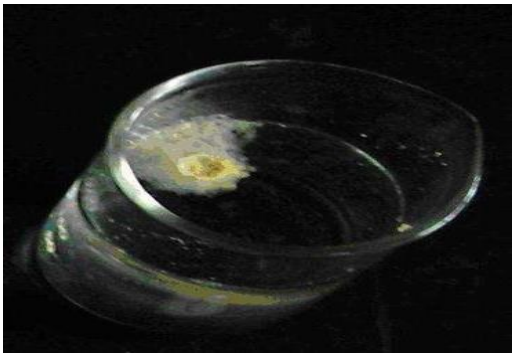

Fig. no.9. After 12 hr

***In vitro* drug release study:**

The release of *A. marmelos* from different formulations were determined using USP Paddle apparatus 2 under sink conditions. The dissolution medium was 900 ml of a 0.1 N HCl solution (pH= 1.2), at 37 ± 0.2ºC at 50 rpm. 10 ml samples were drawn with every one hour upto a period of 20-24 hrs. the samples were diluted suitably and filtered. The required dilutions were made with and the solution was analyzed for the drug content by using UV detector. From this % drug release was calculated and this was plotted against function of to the pattern of drug release. The percentage cumulative drug release of all formulation from F1 to F9 were within the range of 84.70 – 98.13% for 8 hrs (Fig.no.10). from the results of *in vitro* drug release studies, it concludes that F8 had better controlled release than the other formulation.

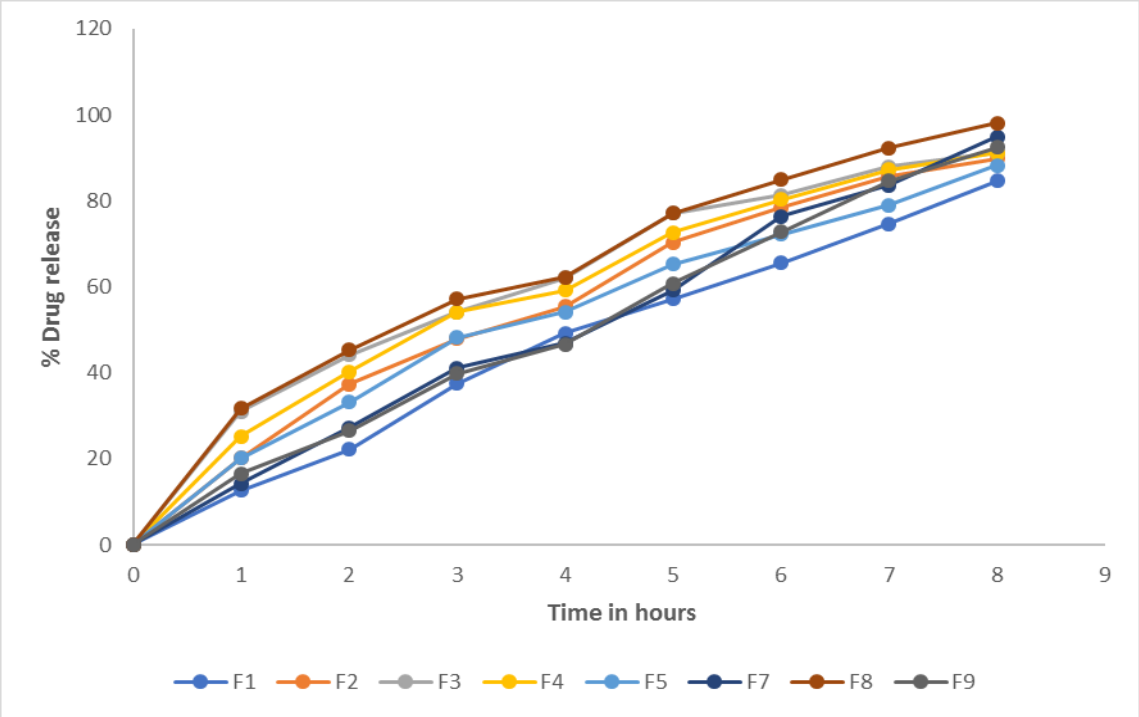

Fig no.10. Percentage of Drug Release

CONCLUSION:

In this study, gastro-retentive herbal floating tablet of *Aegle marmelos* fruit extract can be successfully prepared by using direct compression techniques used in different concentration of polymers. The prepared herbal floating tablet were evaluated for various parameter like disintegration time, drug content, floating lag time (buoyancy time), *in vitro* drug release study, etc. and shows the satisfactory result. The formulation was prepared to reduce the side effects and increase the clinical effects. The optimized formulation was found to be F8 which released 98.13% of drug in 8hr *in vitro*, while the floating lag time was 35 seconds. From this results obtained, it was concluded that formulation F8 containing HPMC K4M & HPMC E15 shows a desirable Sustained effect for 8 hrs having 98.13% release at the end of 8 hours.

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