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ANTIHYPERLIPIDIMIC GASTRO FLOATING TABLET OF PRAVASTATIN PREPARED FROM DIFFERENT GRADES OF HPMC POLYMER

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Abstract:

Oral route is the most convenient route for the drug delivery because of ease of administration, economic therapy & patient compliance. Floating drug delivery system (FDDS) is one of the convenient ways than the convectional oral drug administration which keep drugs buoyant is stomach due to their low density than gastric fluid and can be a potential candidate for controlled release of drug over an extended period of time.

FDDS are expected to maximize the absorption resulting in enhanced bioavailability and prolong residence time of drug in stomach. Pravastatin is an oral hyperlipidemic drug used to reduce blood cholesterol level. Floating tablets of pravastatin were prepared by using direct compression technique. The floating tablets of Pravastatin were prepared with different viscosity grades of HPMC (HPMC K4M, HPMC K15M, and HPMC K100M) and with different drug to polymer ratios. Prepared tablets were evaluated for parameters like friability, hardness, thickness, percentage weight variation, and content uniformity, buoyancy floating lag time, stability studies and in vitro release. Tablets of all formulations were found to be circular with no cracks and were white to off white in colour. The diameter of all formulations ranged between 7.96 to 8.00mm and thickness was in the range of 2.95 to 3.22mm. Stability Studies were carried out at room temperature for 30 days. The physical stability was assessed by the appearance and there was no change in colour or shape of the tablet on storage. F9 formulation containing 80 mg of HPMC K100M was most stable at the end of storage period. Thus, from the results of tablet evaluation it can be concluded that due to the buoyancy of drug in stomach, the prepared pravastin floating tablet maximize the absorption resulting in enhanced bioavailaibility and prolong resident time of drug in stomach.

Key words: *Buoyant tablets, Gastroretentive, floating tablets, pravastatin, sustained release tablets*

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INTRODUCTION:

Oral route is the most convenient route for the drug delivery because of ease of administration, economic therapy & patient compliance. The use of conventional oral dosage form is associated with problems like dose related adverse effect, short duration of action, rapid transit from GIT. To overcome such drawback of oral drug delivery, floating drug delivery concept have evolved and many researcher proposed new dimension for this type of oral dosage form[1].

Attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. Floating drug delivery system (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. These results in an increased gastric retention and a better control of the fluctuations in plasma drug concentration[2]. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also required to keep the dosage form reliably buoyant on the surface of the meal[3,4].

Since FDDS keep drug buoyant is stomach it can be a potential candidate for controlled release of drug over an extended period of time. These systems help in continuously releasing the drug before it reaches to the absorption window, thus ensuring optimal bioavailability. Floating of tablet also minimize the rapid transition of drug from GIT[5].

Controlled release dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and time to achieve peak plasma level. On the other hand, incorporation of the drug in a controlled release gastro-retentive form (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Gastro-retention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastro-retention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients[6,7].

Floating drug delivery systems is retained in stomach and is useful for drugs that are poorly soluble or insoluble in gastric fluids. In this system, the dosage form is less dense than gastric fluids so that it can float. Various floating tablets like Ibuprofen, gliclazide,Furosemide[8], famotidine[9], ranitidine, domperidone maleate[10], mebendazole[11], aceclofenac[12], cefuxime axetil, gabapentin[13], captopril, oflaxacin[14], repaglinide[15], losartan, cephalexin[16] have been reported in literature.

Pravastatin is an oral hyperlipidemic drug used to reduce blood cholesterol level. Pravastatin acts as a lipoprotein-lowering drug through two pathways. In the major pathway, pravastatin inhibits the function of hydroxymethylglutaryl-CoA (HMG-CoA) reductase. As a reversible competitive inhibitor, pravastatin sterically hinders the action of HMG-CoA reductase by occupying the active site of the enzyme.

Pravastatin even when taken at its higher doses (40-80 mg/day) has its t1/2 is 1-3 hours and have side effects like fever, unusual tiredness, and dark colored urine,chest pain; increased thirst, increased urination, hunger, dry mouth, fruity breath odor, drowsiness, dry skin, blurred vision, weight loss etc . In oder to overcome these side effects and to reduce frequency of doses, low dose of pravastatin (20 mg/day) was chosen for preparation of floating tablets.

The aim of present study is to formulate floating tablet of pravastatin which will release the drug for extended period of time, reducing the frequency of administration. Floating of tablet also minimize the rapid transition of drug from GIT.

MATERIALS AND METHOD:

MATERIALS

Pravastatin supplied as a gift sample from Micro Lab Bangalore, India. HPMC and methanol are purchased from G.S. Chemical Testing Lab & Allied Industries, Bombay and HCL was purchased from Ranbaxy Fine Chemicals Ltd., New Delhi. All other reagents and solvents were of analytical grade and purchased from local suppliers unless stated otherwise.

Drug- excipient compatibility studies by FTIR

A physical compatibility test was carried out to determine drug excipient interactions. The physical mixture, 1:1 ratio of drug and excipient were uniformly prepared. The mixture was placed in glass vials which were kept at room temperature. After 15 days samples were evaluated for colour/ appearance for compatibility testing [17].

Table 1: Formula of pravastatin floating tablet preparation

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pravastatin	20	20	20	20	20	20	20	20	20
HPMC K4M	40	60	80	-	-	-	-	-	-
HPMC K15M	-	-	-	40	60	80	-	-	-
HPMC K100M	-	-	-	-	-	-	40	60	80
Sodium bicarbonate	20	20	20	20	20	20	20	20	20
Citric acid	5	5	5	5	5	5	5	5	5
Dicalcium phosphate	15	15	15	15	15	15	15	15	15
Lactose	80	60	40	80	60	40	80	60	40

Fourier transform Infra red analysis (FT-IR)measurements of pure drug, polymers and drug loaded floating tablets formulations were obtained using a model name BX- Perkinelmer System 200FT-IR Spectrophotometer. The pellets were prepared on KBr press under hydraulic pressure of 150 kg /cm^2, the spectra were scanned over the wave number range of 4000-400 cm-1 at an ambient temperature [12].

The Fourier Transform Infrared spectroscopy (FTIR) was employed to characterize the possible interaction between the drug and excipient in the solid state. It was recorded using FTIR spectrophotometer.

Formulation development

Preparation of floating tablets

The floating tablet was prepared by direct compression method [18]. Polymers selected for tablets are HPMC K4M, HPMC K15M, and HPMC K100M. Other excipients like Dicalcium phosphate, Lactose, Sodium bicarbonate, citric acid anhydrous, Magnesium Stearate were selected for the study. Citric acid was also used as an antioxidant. The floating tablets were prepared by various formulae given in table 1[19].

Matrix tablets each containing 20 mg of pravastatin were formulated employing (i) HPMC K100M (ii) HPMC K4M and (iii) K15M, each at 40 and 60 and 80% concentration in the formula. Sodium bicarbonate was used as gas generating agent at 20%, strength in each case[20]. The required quantities of pravastatin, HPMC K100M or HPMC K4M, sodium bicarbonate, lactose were thoroughly mixed in a mortar by following geometric dilution technique[21,22]. Mixture of water and alcohol in 1: 1 ratio was used as granulating fluid. The fluid was added and mixed thoroughly to form a dough mass. The mass was passed through mesh No.12 to obtain wet granules. The wet granules were dried at 60^0C for 2 h. The dried granules were passed through mesh No. 16 to break the aggregates. The lubricants talc (2%) and magnesium stearate (2%) were passed through mesh No. 60 on to the dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a 16-station tablet punching machine (M/s Cadmach Machinaries Pvt. Ltd., Ahmedabad).

Evaluation of Tablets

The prepared floating pravastatin tablets were evaluated for weight variation, hardness, thickness, diameter, friability, content uniformity, lag time, *in-vitro* drug release studies and stability studies.

1. Weight variation:

Weight variation test was done as per USP method. The test was carried out by weighing 20 tablets individually using analytical balance, then calculating the average weight, and comparing the individual tablet weights to the average[23].

2. Hardness and Thickness:

Hardness was measured using Monsanto hardness tester, for each batch twenty tablets were tested. Thickness was done by using screw- gauge micrometer. Twenty tablets from each batch were randomly selected and thickness was measured[14].

3. Friability:

Friability was determined according to British Pharmacopoeia[24] with Roche friabilator. Twenty tablets were weight and placed in the Roche friabilator and it was operate 25 rpm for 4 min. After revolution the tablet were weighted and calculated the percentage friability.

4. Content uniformity:

Twenty tablets were crushed in a mortar and the powder equivalent to 100mg of drug was weighed

and dissolved in 100 ml of solvent, and aliquots were prepared. The solution was diluted suitably and analyzed for drug content by Thermo scientific, evaluation 201- UV spectrophotometer.

5. Lag time:

In vitro buoyancy was determined by floating lag time as per the method described[25]. The tablets were placed in a 100ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time[26].

6. *In vitro* drug release studies:

The in vitro drug release study of various batches was carried out using USP-Type II dissolution apparatus (paddle type) for 24 hrs. The dissolution medium, 900 ml of pH 1.2 phosphate buffer solutions, was placed into the dissolution flask maintaining the temperature of 37±0.5^{0}C at 100 rpm. 5 ml of sample was withdrawn at various time intervals and replaced by the respective buffer solutions. Samples withdrawn were analyzed by UV spectrophotometer at 238nm at pH 1.2 for estimation of amount of drug released using buffer solution as blank[23].

7. Stability studies:

The selected formulation was subjected for stability studies up to 3 months as per ICH guidelines at room temperature (25±2^{0}C/60%±5%RH). The percentage drug un-decomposed was studied after every month[17].

RESULTS AND DISCUSSION:

Drug excipient compatibility studies

The drug excipient interaction studies revealed no significant physical changes were observed in colour, appearance. The overlay FTIR spectra of various physical mixtures are shown in figure 1. FTIR spectra of pravastatin showed all the peaks corresponding to the functional groups present in the structure of pravastatin. As depicted in figure 1. The characteristic absorption peaks of pravastatin were obtained at 3546 cm^{-1} due to O-H stretching , 2924 cm^{-1} due to Methyl C-H symmetric stretch, Methylene C-H asymmetric stretch, 1697 cm^{-1} due to Ester C=O stretch, associated, 1461 cm^{-1} due to Methylene C-H symmetrtic bend, Methyl C-H asymmetric bend, 1268 cm^{-1} due to Lactone –C-O-C bend, 1164 cm^{-1} due to Ester –C-O-C- bend. These peaks have also been observed in the physical mixture of drug and excipients[17]. It can be concluded that the excipients as the endothermic peaks remained unchanged in position. From the observation of FTIR study, it was concluded that the excipients and drug did not interact with each other and are compatible.

Table2: Evaluation of Pravastatin floating tablets

Batch	Weight variation (g)*	Hardness Kg/cm^{2*}	Thickness (mm)*	Diameter (mm)*	Average Friability (%)	Average Content Uniformity (%)
F1	0.20±0.08	6.22±0.13	3.05±0.06	8.00±0.01	0.23	94.32
F2	0.20±0.05	6.03±0.18	3.22±0.08	7.99±0.06	0.42	97.42
F3	0.20±0.06	6.15±0.19	3.17±0.11	7.96±0.04	0.36	99.10
F4	0.20±0.06	6.15±0.23	2.95±0.05	7.99±0.01	0.32	98.20
F5	0.19±0.05	6.14±0.13	3.13±0.06	7.99±0.016	0.18	96.75
F6	0.20±0.06	6.01±0.17	3.02±0.12	7.98±0.09	0.45	99.38
F7	0.20±0.05	6.11±0.11	3.02±0.03	7.97±0.07	0.62	97.04
F8	0.21±0.05	5.91±0.23	2.99±0.08	7.96±0.09	0.51	97.16
F9	0.19±0.07	6.03±0.26	3.00±0.06	7.99±0.02	0.38	98.30

*All values represent n=3

Table 3: Floating lag time

Batch	Floating lag time (sec.)*
F1	8.45±0.13
F2	28.42±0.43
F3	97.74±0.94
F4	12.87±0.83
F5	11.56±0.68
F6	17.80±0.61
F7	52.07±1.59
F8	10.32±0.31
F9	87.85±1.02

*All values represent n=3

Evaluation of tablets

The tablets were prepared by direct compression method reported by Kwakye et al. [18] and were evaluated for various parameters given in table 2. The weight variation of various formulation (F1 to F9) was found to be 0.20±0.08, 0.20±0.05, 0.20±0.06, 0.20±0.06, 0.19±0.05, 0.20±0.06, 0.20±0.05, 0.21±0.05, 0.19±0.07 g respectively (Yin et al, 2013)[16]. Hardness was measured using Monsanto hardness tester, the hardness for formulation coded F1 to F9 was found to be 6.22±0.13, 6.03±0.18, 6.15±0.19, 6.15±0.23, 6.14±0.13, 6.01±0.17, 6.11±0.11, 5.91±0.23, 6.03±0.26 Kg/cm^2, respectively. This indicates adequate mechanical strength. Thickness was found to be 3.05±0.06, 3.22±0.08, 3.17±0.11, 2.95±0.05, 3.13±0.06, 3.02±0.12, 3.02±0.03, 2.99±0.08, 3.00±0.06 mm formulation (F1to F9). The Diameter of all formulations (F1to F9) was found to be 8.00±0.01, 7.99±0.06, 7.96±0.04, 7.99±0.01, 7.99±0.016, 7.98±0.09, 7.97±0.07, 7.96±0.09, 7.99±0.02 mm. Friability was determined according to British Pharmacopoeia with Roche friabilator. The friability was found to be all formulation were obtained as F1 to F9 formulation respectively 0.23%, 0.42%, 0.36%, 0.32%, 0.18%, 0.45%, 0.62%, 0.51%, and 0.38 %. The content uniformity was obtained from various formulations (F1 to F9) 94.32%, 97.42%, 99.10%, 98.20%, 96.75%, 99.38%, 97.04% and 97.16%.

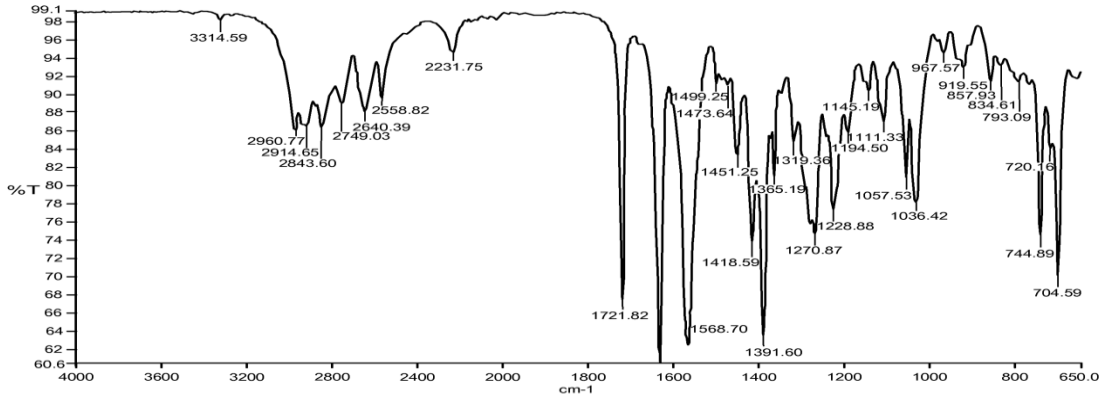

Fig 1: FTIR spectra of pravastatin

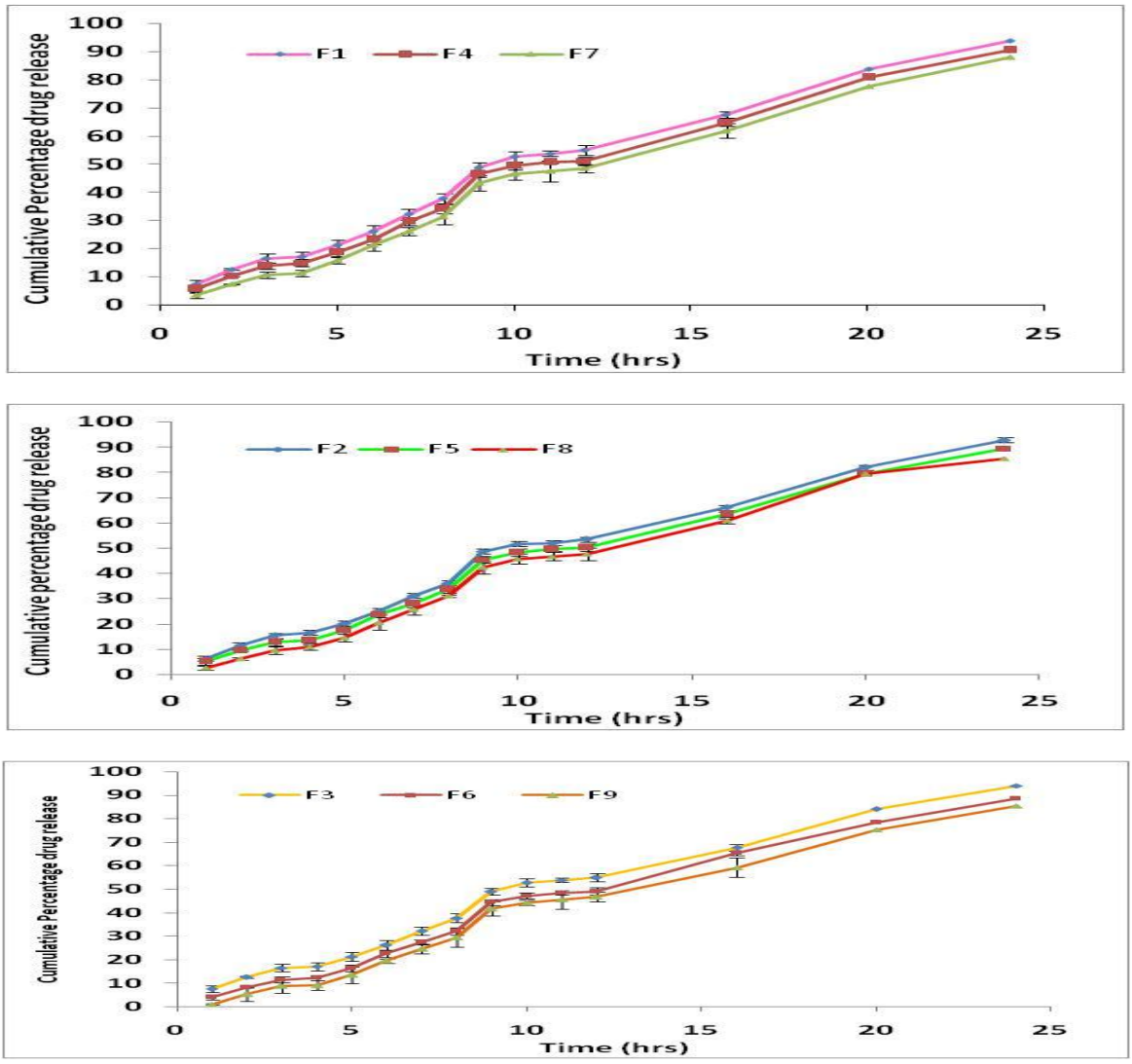

Fig 2: Comparative Dissolution release profile of Pravastatin with different batches

In-vitro Dissolution studies using SGF of pH 1.2

The graph of drug release is shown in figure2. Tablets were evaluated for in- vitro release characteristics for 24 hrs. Batch F1, F2, and F3 showed release 93.99±1.33%, 92.8±1.2%, and 92.86±1.27% at 24 hr. respectively. Batch F4, F5, F6 showed release 90.65±1.13%, 89.54±1.07%, and 88.48±1.04% respectively. Batch F7, F8, F9 showed release87.9±06%, 80.6±1% and 85.4±41% respectively. Therefore from the dissolution graphs for all the batches, it is concluded that, as the concentration of all batches the release retardant polymers increases, the drug release is sustained[7].

In vitro buoyancy study/ Floating study

In vitro buoyancy was determined by floating lag time as per the method described[25]. The tablets were placed in a 100ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time. The floating lag time was found to be all formulation were obtained as F1 to F9 formulation respectively8.45±0.13, 28.42±0.43, 97.74±0.94, 12.87±0.83, 11.56±0.68, 17.80±0.61, 52.07±1.59, 10.32±0.31, 87.85±1.02 second.

Stability studies

The selected formulation was subjected for stability studies up to 3 months as per ICH guidelines at room temperature (25 ± 2^0C/60%±5%RH). The result of the stability study does not indicate any significant changes in the drug content.

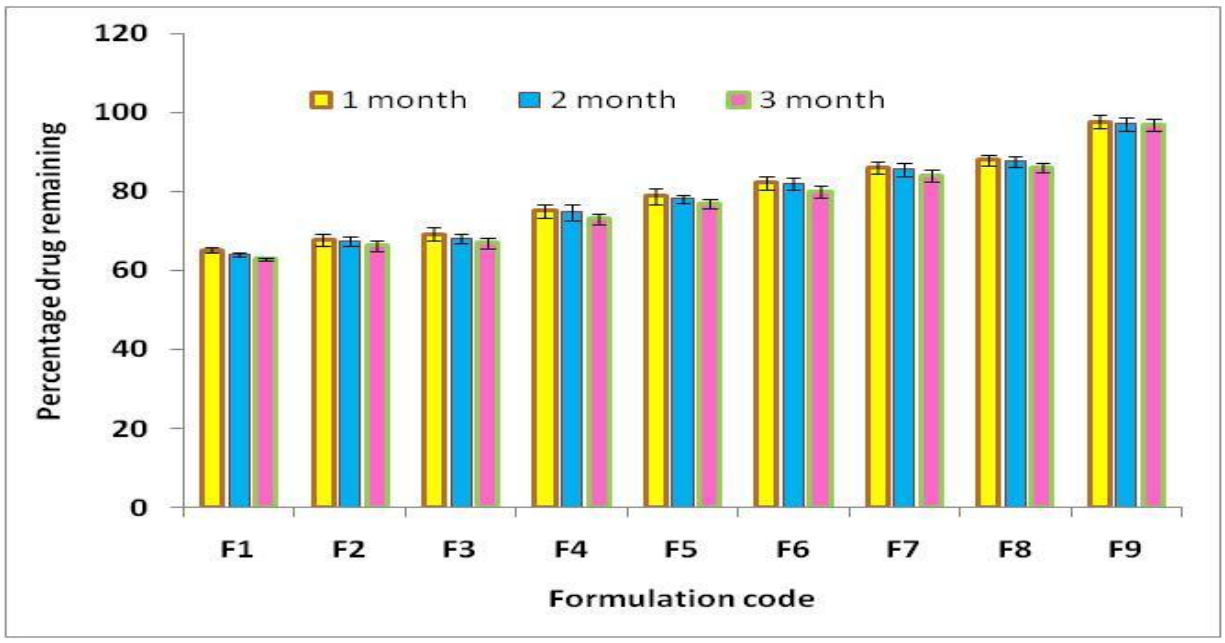

Fig 3: Percentage drug remaining in different formulations after storage at 25±2^{0}C/60%±5%RH

CONCLUSION:

Pravastatin floating tablets were prepared and evaluated. The tablets showed acceptance ranges of parameters like weight variation, hardness, thickness, friability and drug content and buoyancy studies. The sustained release of drugs was achieved using by different retardant polymers like HPMC K4M, HPMCK15M, and HPMCK100M. Batch F2 showed better result as compared to other batches. Floating drug delivery system keep drugs buoyant is stomach due to their low density than gastric fluid and can be a potential candidate for controlled release of drug over an extended period of time. FDDS are expected to maximize the absorption resulting enhanced bioavailability and prolong the residence time of drug in stomach. These systems help in continuously releasing the drug before it reaches to the absorption window, thus ensuring optimal bioavailability. It is concluded that due to the buoyancy of drug in stomach to their low density than gastric fluid, the prepared pravastin floating tablet maximize the absorption. Resulting enhanced bioavailability and prolongs resident time of drug in stomach.

CONFLICT OF INTEREST: All the authors report no conflict of interest

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REFERENCES:

1.Pawar HA and Dhavale R, Development and evaluation of gastroretentive floating tablets of an antidepressant drug by thermoplastic granulation technique, Beni-Suef University Journal of Basic and Applied Sciences, 3(2)122-132, 2014.

2. Dhiman S, thakur GS , Rehni AK, sood S, Arora S, Gastroretentive a Controlled release drug delivery system, Asian Journal of Pharmaceutical and Clinical Research, 4,(1) , 5-13, 2011.

3. Kavitha K, Narendra CT, Rajesh G, Ramesh S, Shivaleela P, Lavanya and Premalatha. Formulation and evaluation of ranitidine floating tablets, International journal of pharmaceutical, chemical and biological sciences, 3(3), 761-766, 2013.

4. Baru CR, Vidyadhara S, Rao RKV, Prakash V K and Umashankar B. Formulation and evaluation of ibuprofen floating tablets, International Journal of Pharmaceutical, Chemical and Biological Science, 2(4), 472-481, 2012.

5. Singh S, Prajapati K, Pathak AK, and Mishra A. Formulation and Evaluation of Floating Tablet of Captopril, International Journal of Pharm. Tech. Research Coden (USA), 3, 333-341, 2011.

6. Meka VS, Rao NS, Songa AS, Battu JR, Kolapalli VRM, Statistical design and evaluation of a

propranolol HCl gastric floating tablet ,Acta Pharmaceutica Sinica B, 2(1),60–69,2012.
7. Tanwar YS, Jamini M, and Srivastava B, Formulation and In Vitro Evaluation of Floating Tablets of Losartan Potassium, Mahidol University Journal of Pharmaceutical Sciences, 40 (2), 17-24, 2013.
8. Darandale SS, and Vavian PR, Design of a gastroretentive mucoadhesive dosage form of furosemide for controlled release, Acta Pharmaceutica Sinica B, 2(5), 509–517, 2012.
9. Gupta R, Prajapati SK, Pattnaik S, Bhardwaj P, Formulation and evaluation of novel stomach specific floating microspheres bearing famotidine for treatment of gastric ulcer and their radiographic study, Asian Pacific Journal of Tropical Biomedicine, 4(9), 729-735, 2014.
10. Saritha D, Sathish D, Madhusudan YR, Formulation and Evaluation of Gastroretentive Floating Tablets of Domperidone maleate. Journal of Applied Pharmaceutical Science,2 (3),20 68-73, 2012
11. Patel MK, Biswal B, Karna N, and Patel J, Preparation and evaluation of gastro retentive floating tablets of Mebendazole , International Journal of Current Pharmaceutical Research , 3 (1) , 63-65, 2011.
12. Reddy AB, Samyuktha BR, Eswar DT, Sivanaga RD, Sindhura L, Sarath NK,Aceclofenac floating tablets - a promising sustained release dosage form, International Journal of Drug Development & Research, 3(2) ,121-127, 2011.
13. Ranjan kar N, mahapatra SK, Pothal RK, and Meher CP Formulation and in vitro evaluation of tablet of gabapentin, Reserch Journal Pharm. and tech. 9(1), 11-16,2016.
14. Sheth NS and Mistry RB, Formulation and evaluation of floating drug delivery system, International journal of pharm. and bio sciences, 2(1), 571-580, 2011
15. Shakya R, Thapa P and Saha RN, In vitro and in vivo evaluation of gastroretentive floating drug delivery system of ofloxacin, Asian Journal of Pharmaceutical Sciences, 8, 191-198, 2013.
16. Yin L, Qin C, Chen K, Zhu C, Cao H, Zhou J, He W, and Zhang Q, Gastro-floating tablets of cephalexin Preparation and *in vitro/in vivo* evaluation, International Journal of Pharmaceutics,452 (1-2)241-248, 2013.
17. Mandlik SK, Dixit AA, Gujar KN, Formulation and in vitro evalution of sustained release matrices of eprisone hydrochloride, Inveti Journal pharm tech,4,183-187, 2015.
18. Kwakye KO, Mfoafo KA, Kipo SL, Kuntworbe N, -Gyasi King ME, Development and evaluation of natural gum-based extended release matrix tablets of two model drugs of different water solubilities by direct compression, Saudi Pharmaceutical Journal, 24, 82–91, 2016.
19. Rao GK Mandapalli PK, Manthri RP, Reddy VP, Development and in vivo evaluation of gastro - retentive delivery systems for cefuroxime axetil, Saudi Pharmaceutical Journal, 21, 53–59, 2013.
20. Dios P, Pernecker T, Nagy S, Pal S , Devay A, Influence of different types of low substituted hydroxypropyl cellulose on tableting, disintegration, and floating behavior of floating drug delivery systems, Saudi Pharmaceutical Journal ,23, 658–666, 2015.
21. Chowdary KPR and Hussainy SA, Formulation and evaluation of floating tablets of gliclazide employing HPMC and carbopol, International Journal of Chemistry Science, 10(3), 1213-1220, 2012.
22. Sharma M, Kohli S and Dinda A, In-vitro and in-vivo evaluation of repaglinide loaded floating microspheres prepared from different viscosity grades of HPMC polymer, Saudi Pharmaceutical Journal,23 (6), 675-682, 2015
23. United States Pharmacopeia- National formulary, published by USP33-NF28, R76-R88, 2010.
24. British pharmacopoeia, published by the stationary office on behalf of the medicine and health care products regulatory agency, volume fifth, page no. A457, 2011.
25. Rosa M, Zia H, Rhodes T, Dosing and testing in vitro of a bioadhesive and floating drug delivery system for oral application. International Journal of Pharm. 105, 65–70, 1994.
26. Klausner EA, Lavy E, Friedman M, Hoffman A, Expandable gastroretentive dosage forms, Journal of Controlled Release, 90, 143–162, 2003.