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Studies on Gastro Retentive Clopidrogrel Tablets for Peripheral Vascular Disease Treatment

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ABSTRACT

The purpose of present work was for formulation and characterization of Clopidrogrel floating tablets to improve bioavailability and to minimize the side effects of the drug. FTIR studies were conducted for drug polymer compatibility. The Clopidrogrel sustained release floating tablets were formulated by wet granulation method. Tablets were subjected to pre and post compressional evaluation studies. The different concentrations of HPMC K4M, HPMC K15M, xanthan gum, guargum, and sodium bi carbonate 25% w/w is used as gas generating agent and micro cellulose crystalline MCC are used in different concentrations (75%, 50%, 25%) as diluent. The tablets were tested for thickness, weight variation, hardness, friability, drug content; *In vitro* floating parameters and drug release studies were also conducted. Compatibility studies revealed that there is no interaction between drug and polymers in the formulations. The flow properties were within the limits and the granular bed exhibited uniform flow and ease for compression. Clopidogrel floating tablets showed uniform post compressional properties with minimum standard deviation. The formulations showed minimum floating lag time and prolonged duration of floating. *In vitro* drug release of clopidogrel was sustained up to 12 h. Clopidrogrel release followed zero order, first order, Higuchi drug release kinetics for drug release. The peppas diffusion coefficient ranged from 0.455 - 0.895 indicating drug release by non fickian diffusion followed by erosion. The F4 floating tablet was optimized formulation which showed 100% release sustained for 12 h. The stability studies indicated stability of drug in the optimized formulation against temperature and humidity.

Keywords: Clopidrogrel, Floating tablets, HPMC K15M, Xanthan gum, guar gum, Release kinetics, Stability studies.

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INTRODUCTION

Gastro retentive drug delivery systems (GDDS)

Development of oral controlled-release systems has been a challenge to formulation scientists because of their inability to restrain and localize the system in the targeted area of the gastrointestinal tract. Controlled/sustained release preparations using alternative routes have been formulated but the oral route still remains preferable. When the drug is formulated with a gel forming polymer such as semi synthetic derivatives of cellulose, it swells in the gastric fluid with a bulk density less than one [1-3]. The concept of FDDS was first discovered by Davis in 1968 after few reports of gagging or choking by few patients, while swallowing medicinal pills. The researchers suggested that such difficulty could be overcome by providing pills having a density of less than 1.0 g/ml, so that pill will float on water surface. Since then several approaches have been proposed for ideal floatable delivery system, these buoyant delivery systems include hollow microspheres (micro balloons), granules, tablets (pills) capsules and laminated films [4-6].

Approaches to increase gastric retention

Various approaches have been worked out to improve the retention of an oral dosage form in the stomach, e.g. floating systems, swelling and expanding systems and other delayed gastric emptying devices. Floating drug delivery systems have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after complete release of the drug the residual system is expelled from the stomach. This leads to an increase in the gastric residence time (GRT) and a better control over fluctuations in plasma drug concentration. Swellable systems include the products that swell after swallowing to an extent that prevents their exit from the stomach through the pylorus. This results in retention of dosage form in stomach for prolonged period. These systems may be called plug type systems as they show a tendency to remain lodged at the pyloric sphincter. Modified systems are non disintegrating geometric shapes made up of silastic elastomer or extruded from polyethylene blends, which prolong the GRT, depending on size and shape. High density gastro retentive systems include coated pellets that have a density greater than the stomach contents (average1.004 g/cm^3). This can be achieved by coating the drug or systems with heavy inert material such as zinc oxide, titanium oxide, barium sulphate etc. Other approaches for delayed gastric emptying include feeding of some indigestible polymers of fatty acid, which can change the motility of GI tract and hence prolonged drug release. [7-10]

Effervescent FDDS

These floating delivery systems employ matrices from swelling polymers like Methocel or Chitosan and effervescent components such as sodium bicarbonate and tartaric acid or citric acid or matrices having chambers of liquid components that gasify at body temperature. The matrices are prepared in such manner that when they come in contact with stomach fluid, carbon dioxide is generated, and retained entrapped in the hydrocolloid gel. This leads to an upward drift of the dosage form and maintains it in a floating condition. A single layer tablet may be compressed in which gas liberating component is present in hydrocolloid layer and the drug is compressed in other layer for sustained release [11-16].

Peripheral vascular disease

Peripheral vascular diseases (PVDs) are circulation disorders that affect blood vessels outside of the heart and brain. In PVD, blood vessels are narrowed. Narrowing is usually caused by arteriosclerosis. Plaque decreases the amount of blood and oxygen supplied to the arms and legs. Eventually, arteries can become obstructed. PVD that develops only in the arteries is called peripheral arterial disease (PAD). This is the most common form of PVD. Approximately 12 to 20 percent of people over age 65 have PAD. PVD and PAD are often used to mean the same condition. There are two main types of PVD: Functional PVD and Organic PVD. [17-19]

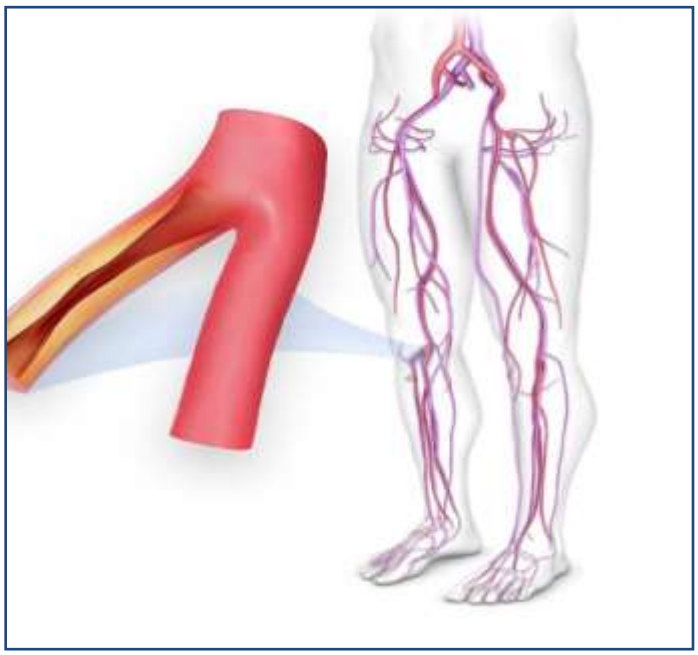

Figure 1: Peripheral vascular disease

Diagnosis, treatment and drugs used

*Measuring the pulses in legs and feet, Doppler ultrasound***,** Ultrasound, *Ankle-brachial index (ABI), Pulse volume recording (PVR)***,** *Angiography, Magnetic resonance angiography (MRA) and*

computerized tomography angiography (CTA). Treatment typically includes lifestyle modifications like stop smoking, regular exercise program includes walking, balanced diet with proper nutrition, lose weight, treat conditions such as diabetes, high blood pressure, or high cholesterol. Smoking cessation is one of the most important ways to treat PVD. Smoking directly causes reduced blood flow in vessels. Cilostazol or pentoxifylline to increase blood flow to the legs, ease leg pain, and relieve symptoms of claudication. Clopidrogel or daily aspirin to reduce risk of blood clots. Clots could cut off the blood supply to a limb leads to risk of amputation. Atorvastatin, simvastatin, or other statins to lower high cholesterol. Angiotensin-converting enzyme (ACE) inhibitors to lower high blood pressure.[18, 19]

MATERIALS AND METHODS

Clopidogrel was procured as gift samples from Pharma Train labs, (Hyderabad), HPMC K100M, HPMC K15M, Xanthan gum, Guar gum supplied by colorcorn (Mumbai), Magnesium Sterate and Avicel Ph102(MCC) from FMC Bio Polymer (Mumbai), Sodium Bicarbonate, Talc, Methanol and ethanol from S.D. Fine Chemicals (Mumbai), All the materials used in the study were of analytical and laboratory grade.

Determination of λ_{max} of Clopidogrel in 0.1N HCl

Working standard: 50 mg of Clopidogrel was weighed and dissolved in 50ml 0.1N HCl and then made up to a volume of 50ml with0.1N HCl it give 1000 µg/ml concentrated stock solution. From the working standard solution 1ml was diluted to 100 ml with 0.1NHCl it will give 10 µg/ml concentrated solution. This solution was scanned at range of 200-400 nm wavelengths light corresponding scan spectrum curve was noted. The corresponding wavelength having highest absorbance is noted as $\lambda_{max.}$ [20-22]

Construction of calibration curve of Clopidogrel in 0.1N HCl

50mg of Clopidogrel was weighed and dissolved in 50ml 0.1N HCl and then made up to a volume of 50ml with 0.1N HCl it give µg/ml concentrated stock solution. From the working standard solution 1ml was diluted to 100ml with 0.1N HCl it will give 10 µg/ml concentrated solution. From dilution 1, take 1,2,3,4,5 ml of solution and was diluted up to mark in 10ml volumetric flask to obtain 10, 20, 30, 40, 50 µg/ml concentrated solutions. This solutions absorbance was noted at λ_{max} 248 nm. [20-22]

Preformulation Studies

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in rational

development of dosage form. [23]

Compatibility studies (Fourier Transform Infrared Spectroscopic studies)

The drug-excipient interaction study was carried out using by KBr pellet method. To study the compatibility of various formulation excipients with Clopidogrel, solid admixtures were prepared by mixing the drug with formulation excipient separately and it was filled and characterized by using Fourier transform infrared spectroscopy (FTIR). [24]

Formulation of gastro retentive floating tablets by Dry granulation method

Processing steps involved in Dry granulation method: The matrix tablets were prepared by following the General Methodology as given below: All ingredients (Clopidogrel + Avicel PH 102 + polymer) were weighed accurately and co sifted by passing through #22 sieve, blended in a Polybag for 5 min. The above granules were lubricated with # 40 Sieve passed talc. The final blend was then compressed into tablets using 16 station tablet compression machine with an average hardness of 4.0 KP, by using 8 mm die cavity. [25]

Table 1: Formulation table of Clopidogrel floating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Clopidogrel	98	98	98	98	98	98	98	98	98	98	98	98
HPMC K4M	50	75	100	-	-	-	-	-	-	-	-	-
HPMC K15 M	-	-	-	50	75	100	-	-	-	-	-	-
Xanthan Gum	-	-	-	-	-	-	50	75	100	-	-	-
Guar Gum	-	-	-	-	-	-	-	-	-	50	75	100
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Sodium Bi Carbonate	25	25	25	25	25	25	25	25	25	25	25	25
MCC	75	50	25	75	50	25	75	50	25	75	50	25

Evaluation of rheological properties of powder bed[26-28]

Bulk density

Bulk density was determined (Konark instruments, India) by placing the powder/granules blend in a measuring cylinder and the total volume was noted. The weight of powder/granule bed was determined in a Dhona 200 D electronic balance. Bulk density was calculated by using the formula; Bulk density = Total weight of powder or granules / Total volume of powder / granules; Average of three densities of powder/granule were taken and tabulated (n=3). [26]

Compressibility index

Compressibility index was determined by placing the powder/granules in a measuring cylinder and the volume (V_0) was noted before tapping. After 100 tapping again volume (V) was noticed. Compressibility index = (1- V/ V_0) X 100; Where V_0 = volume of powder/granules before tapping,

V = volume of powder/granules after 100 tappings. Average of three compressibility indices of powder/granule readings were taken and tabulated (n = 3). [27]

Table 2: Compressibility Index (%), Flow and Hausner's Ratio

Compressibility Index (%)	Flow	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Angle of repose (°θ)

Angle of repose was determined by measuring the height and radius of the heap of the powder/granule bed. A cut stem funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the plane. Powder/granule was placed in the funnel and allowed to flow freely. With the help of vernier calipers (Mitutoyo, Japan) the height and radius of the heap were measured and noted. Average of triplicate reading were noted (n = 3); Tan ø = h /r; Where h = height of heap of powder/granule bed and r = radius of heap of powder/granule bed. [28]

Table 3: Relationship between nature of flow and Angle of Repose

Flow Property	Angle of Repose
Excellent	25–30
Good	31–35
Passable	>45
Very poor	>65

Evaluation of Compressional characteristics of the tablets: [29-34]

Weight Variation: 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage. Average weight = weight of 20 tablets / 20; The % weight variation = average weight - weight of each tablet / Average weight ×100. Acceptance criteria for tablet weight variation (USP 29-NF 34).

Table 4: Average weight of tablet (mg) and the % Difference allowed in I.P

Average weight of tablet (mg)	% Difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

Thickness test: The tablets were evaluated for their thickness using a micrometer (Mitutoyo, Japan). Average of three readings were taken and results were tabulated (n = 3). [29]

Diameter test: The tablets were evaluated for their diameter using a micrometer (Mitutoyo, Japan). Average of three readings were taken and tabulated (n = 3). [30]

Hardness test: The tablets were evaluated for their hardness using Pfizer hardness tester. Average of three reading were taken and tabulated (n = 3). [31]

Density measurement: The apparent density of the tablets was calculated from their volumes and masses. The volumes V of the tablets were calculated from their height h and radius r using micrometer. Volume of the tablets was calculated by using the following equation $V = \prod x r^2 x h$. Average of three readings were taken and tabulated (n = 3). [32]

Buoyancy lag time: The buoyancy of tablets was studied at 37 ± 0.5 °C, in 100 ml of 0.1N HCl. A glass beaker containing 100 ml of 0.1N HCl was taken, in which a tablet was placed for observation. The duration of time taken to float the tablet was observed visually. Average of three readings were taken and tabulated (n = 3).[33]

Duration of floating time: A glass beaker containing 100 ml of 0.1N HCl was taken, in which a tablet was placed for observation. The total duration for which a tablet remains floating was recorded as duration of floatation. Average of three readings were taken and tabulated (n = 3). [34]

Matrix integrity: During the period of total floating time the swelled matrix tablets were observed for integrity for 12 h. Weigh and finely powder not less than 20 tablets. Transfer an accurately weighed portion of the powder equivalent to about 10mg of model drug a 10 ml volumetric flask. Add approximately 6ml of 0.1N HCl and shake and sonicate for 10 min to complete the extraction. Dilute the methanol to volume and mix. Pipette 1ml aliquot into a 10ml volumetric flask, dilute with mobile phase to volume, mix and filter. From it withdraw take 1ml aliquot and make up to mark with buffer. Calculate the quantity in mg of model drug in the portion taken by the formula; Assay = test absorbance/standard absorbance x standard concentration/sample concentration x purity of drug/100 x 100

Uniform of drug content: The drug content was performed to check the dose uniformity in the formulation. Randomly ten tablets were weighed and powdered. A quantity equivalent to 100mg of Clopidogrel was added in to a 100ml volumetric flask and dissolved in 0.1N HCl. After suitable dilutions the drug content was determined by UV Spectrophotometer at 248 nm again blank.

***In vitro* Dissolution Study:** 900 ml of 0.1N HCl was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of

$37^0C \pm 0.5^0C$. A tablet was placed in the vessel and was covered; the apparatus was operated up to 12 hrs at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} of 248 nm using a UV-spectrophotometer. A 5 ml of sample was with draw at each time point & replace the same volume of medium. [35]

Table 5: *In vitro* Dissolution studies parameters specifications

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCl
Volume	900 ml
Speed	50 rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	1,2,4,6,8,10,12hr
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	248 nm

***In vitro* Release Kinetics**

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from FDDS was described by using zero order kinetics or first order kinetics. The mechanism of drug release from FDDS was studied by using Higuchi equation and the Peppa's-Korsemeyer equation. [36]

Zero Order Release Kinetics

It defines a linear relationship between the fractions of drug released versus time. $Q=k_0t$. Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.[37]

First Order Release Kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution suggested the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is Log C= Log C_o-kt/2.303. Where C is the amount of drug dissolved at time t, C_o is the amount of drug dissolved at t=0, k is the first order rate constant. A graph of log cumulative of log % drug remaining vs time yields a straight line. [37]

Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time. $Q=K_2t^{1/2}$. Where K_2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent[37].

Korsemeyer Peppa's

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analysed by Peppa's-Korsemeyer equation (Power Law). $Mt/ M_\infty =K.t^n$. Where, Mt is the amount of drug released at time t, M_α is the amount released at time α, M_t/M_α is the fraction of drug released at time t, K is the kinetic constant and n is the diffusion exponent. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log drug release upto 60% against log of time will be linear if the release obeys Peppa's-Korsemeyer equation and the slope of this plot represents "n" value.the kinetic data of the formulations were included. Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. [37]

Table 6: Drug release kinetics mechanism

Diffusion exponent (n)	Mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous (Non- Fickian) diffusion
0.89	Case II transport
n > 0.89	Super Case II transport

Stability studies

Stability studies of pharmaceutical were done as per ICH gudidelines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. Method: Selected formulation was stored conditions at elevated temperatures such as $40^0C\pm2^0C$/75%R±5%RH for 90 days. The samples were withdraw at intervals of 30 days and checked for physical changes, hardness, friability, dug content, floating lag time and percentage drug release[38].

RESULTS AND DISCUSSIONS

Compatibility studies – FT-IR method

Clopidogrel and excipients are subjected to FT-IR spectral analysis. The drug was compatible with excipients since no significant changes were observed in intensity and position of the peaks in the spectra.

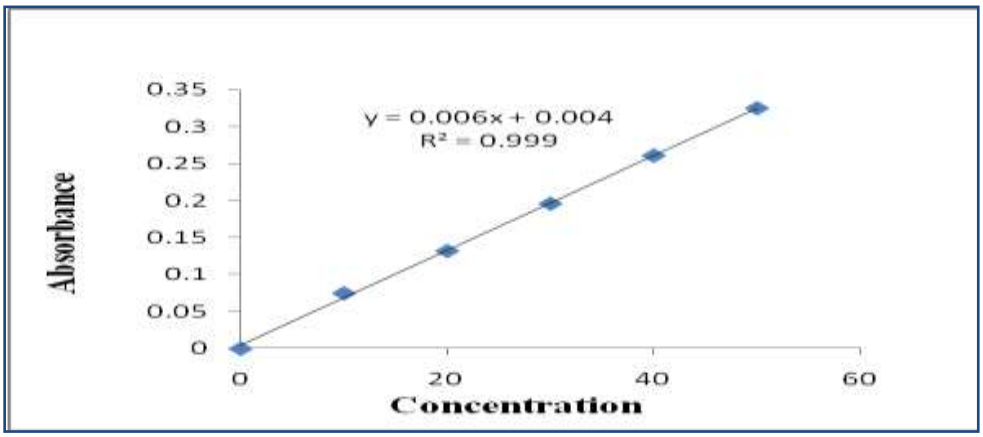

Figure 2: Calibration Curve for Clopidogrel

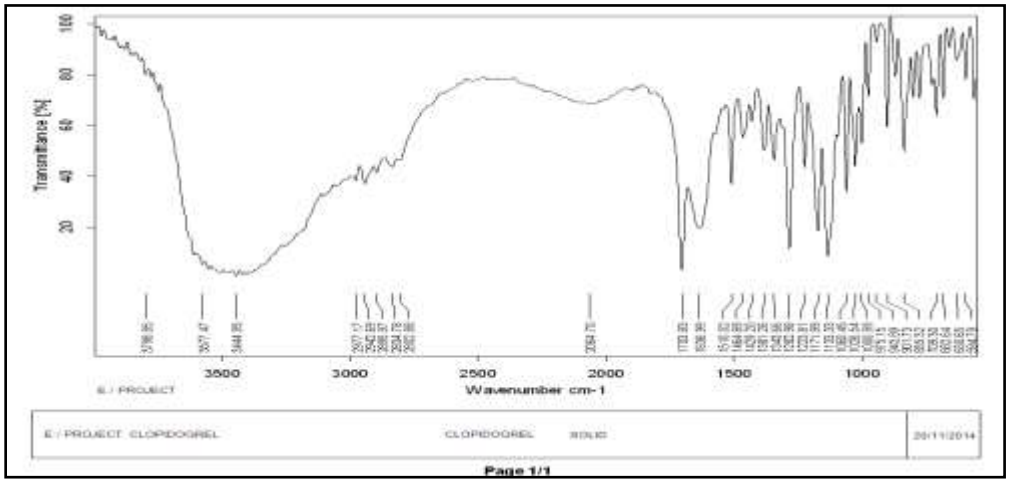

Figure 3: FTIR spectra of Clopidogrel pure drug

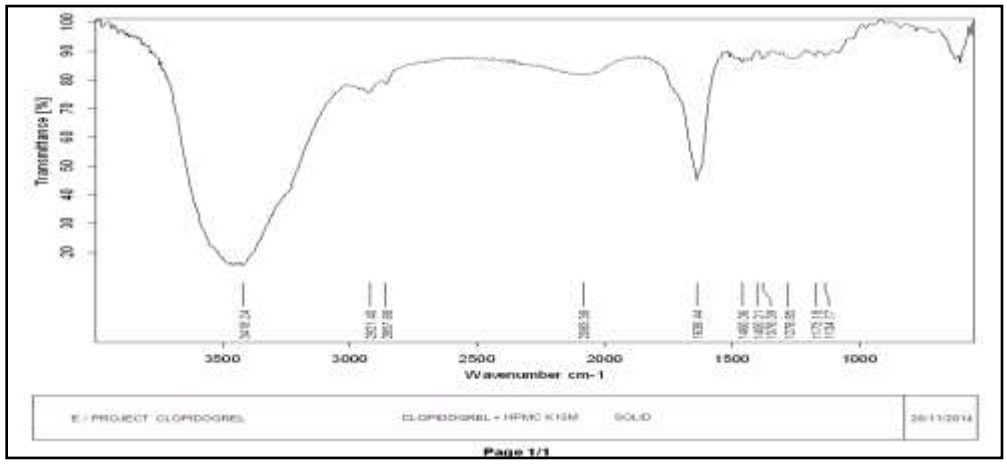

Figure 4: FTIR spectra of Clopidogrel + HPMC K15 M of formulation (F4)

Analytical and compatibility studies

The absorbance of the solution was measured at 248 nm, using UV spectrometer with 0.1N HCl as blank. A graph of absorbance against Concentration was plotted which indicated in compliance to Beer's law in the concentration range 10 to 50 µg/ml (figure 2). The formulation were prepared

with HPMC K4M, HPMC K15M, xanthan gum, guar gum, polymers and then evaluated. The FTIR compatibility studies are conducted on the drug and excipients. Its shows that showed that there was no chemical change or interaction between drug and selected excipient which was evident by the replication of peaks in formulation spectra with that of pure drug indicate physical and chemical compatibility. Hence the above excipients were selected and used for further formulation development. The results were indicated in figure 3-4.

Table 7: Pre-compression parameters of Clopidogrel tablet powder blends

Formulation Code	Bulk density (Kg/cm^3)	Tapped density(Kg/cm^3)	Carr's index	Hausner's ratio	Angle of repose ($^0Ø$)
F1	0.40	0.48	16	1.2	12.73
F2	0.39	0.48	18	1.23	11.96
F3	0.50	0.58	13	1.16	11.58
F4	0.44	0.50	12	1.1	9.92
F5	0.37	0.41	9.75	1.1	12.35
F6	0.37	0.41	9.75	1.1	11.14
F7	0.36	0.39	7.6	1.0	11.03
F8	0.41	0.45	8.8	1.0	11.85
F9	0.39	0.48	18	1.23	11.96
F10	0.41	0.45	8.7	1.0	11.86
F11	0.35	0.40	7.7	1.1	11.04
F12	0.51	0.59	14	1.17	11.59

Pre compression studies

Floating tablets of Clopidogrel was developed to increase the gastric residence time of the drug, so that they can be retained in the stomach for longer time and help in controlled release of drug up to 12 h. Different grades of viscosities of HPMCK4M, HPMCK15M, Xanthan gum, gaur gum polymers is known to be beneficial in improving floating property and release characteristics. The blend prepared by dry granulation and tablets was evaluated for their flow properties; the results for the blends of compression tablets were shown in Table 7. The bulk density and the tapped density for all formulations were found to be almost similar. The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 to 1.23 respectively, indicating good flow and compressibility of the blends. The value of angle of repose for all the formulations was found to be in the range of 9.92-12.73˚ which indicating good flow (i.e. incorporation of glidant will enhance its flow).

Post compression studies

The floating tablets were prepare by dry granulation method using polymers HPMCK4M, HPMCK15M, Xanthan gum, Guar gum to provide sufficient drug release retardation and provide sufficient buoyancy to the tablets. The prepare floating tablets were evaluated for % weight

variation ,thickness, friability, drug content, hardness, all the studies were performed in triplicates and the results were expressed in ± standard deviation. The results have shown in the table 8. The variation in weight was within the range of ±7.5% complying with pharmacopoeia specifications of USP. The thickness of tablets was found to be between 4.9-5.2 mm. The hardness for different formulations was found to be between 3.2 to 5.0 kg/cm^2, indicating satisfactory mechanical strength. The % friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content was found to be within limits 98 to 102 % with standard deviation indicates batch to batch consistency.

Table 8: Post compression parameters evaluation of Clopidogrel tablets F1 - F12

Formulation Code	weight uniformity	Thickness± SD n=3 (mm)	% friability	%Drug Content ± SD	Hardness (Kg/cm^2) ± SD
F1	251±0.31	5.03±0.05	0.132	99.60±1.5	3.63 ±0.057
F2	250±0.45	5.03±0.15	0.143	98.90 ±2.3	3.2 ±0.057
F3	252±0.19	4.93±0.05	0.110	100.2± 1.7	4.7 ±0.101
F4	249±0.27	5.20±0.10	0.133	100.5± 1.4	4.53 ±0.057
F5	252±0.14	5.06±0.11	0.142	101.3 ±1.2	4.56 ±0.057
F6	251±0.37	5.06±0.15	0.151	102.3 ±1.7	5.03 ±0.115
F7	253±0.08	5.03±0.05	0.620	100.1 ±1.2	5.00 ±0.100
F8	250±0.13	5.10±0.10	0.154	100.7 ±1.1	4.63 ±0.057
F9	249±0.22	4.92±0.05	0.111	100.4±1.5	4.69±0.101
F10	250±0.36	5.05±0.15	0.141	99.30±2.3	3.40±0.057
F11	249±0.10	5.01±0.10	0.133	100.5± 1.4	4.53 ±0.057
F12	252±0.43	4.94±0.05	0.112	100.3±1.7	4.69±0.102

Buoyancy studies

The *In vitro* floating behaviour of the tablets was studied by placing them in a beaker containing 0.1 N HCL (pH 1.2). The gas generating agents immediately evolves carbon dioxide in presence of HCl solution generating sufficient porosity which helped the dosage unit to float. The floating lag time was found to be within limits of < 5 min. The formulation F7-F8 prepared with xanthan gum was up to 44 sec and remains buoyant for 10 h till they are completely eroded. On the other hand formulation F10-F12 prepared with gaur gum which shows floating time of 8 h which are eroded. The formulations having matrix integrity and total floating time was up to 12 h (i.e. With HPMC K4M as F1, F2, F3 and With HPMC K15M as F4, F5, F6). This might be due to high viscosity polymer HPMC K4M and HPMC K15M maintains the integrity of the tablets for longer duration by reducing the effect of erosion thus resulting in increase in floating time. The results are show in table 9 and figure 5. Thus it can be concluded that the batches containing HPMC polymers showed good floating lag time and total floating time.

Table 9: *In vitro* Buoyancy Studies of Model drug floating tablets

Formulation Code	Floating lag time (n=3)	Total floating time (n=3)	Matrix Integrity Up to 12 h. (n=3)
F1	19 sec±0.32	Up to 12 h	Non eroding
F2	31 sec±0.52	Up to 12 h	Non eroding
F3	31 sec±0.32	Up to 12 h	Non eroding
F4	19 sec±0.72	Up to 12 h	Non eroding
F5	19 sec±0.21	Up to 12 h	Non eroding
F6	32 sec±0.35	Up to 12 h	Non eroding
F7	44 sec±0.15	Up to 7 h	Eroding
F8	13 sec±0.38	Up to 10 h	Eroding
F9	24sec±0.52	Up to 10 h	Eroding
F10	29sec±0.42	Up to 4 h	Eroding
F11	36sec±0.52	Up to 8 h	Eroding
F12	19 sec±0.21	Up to 5 h	Eroding

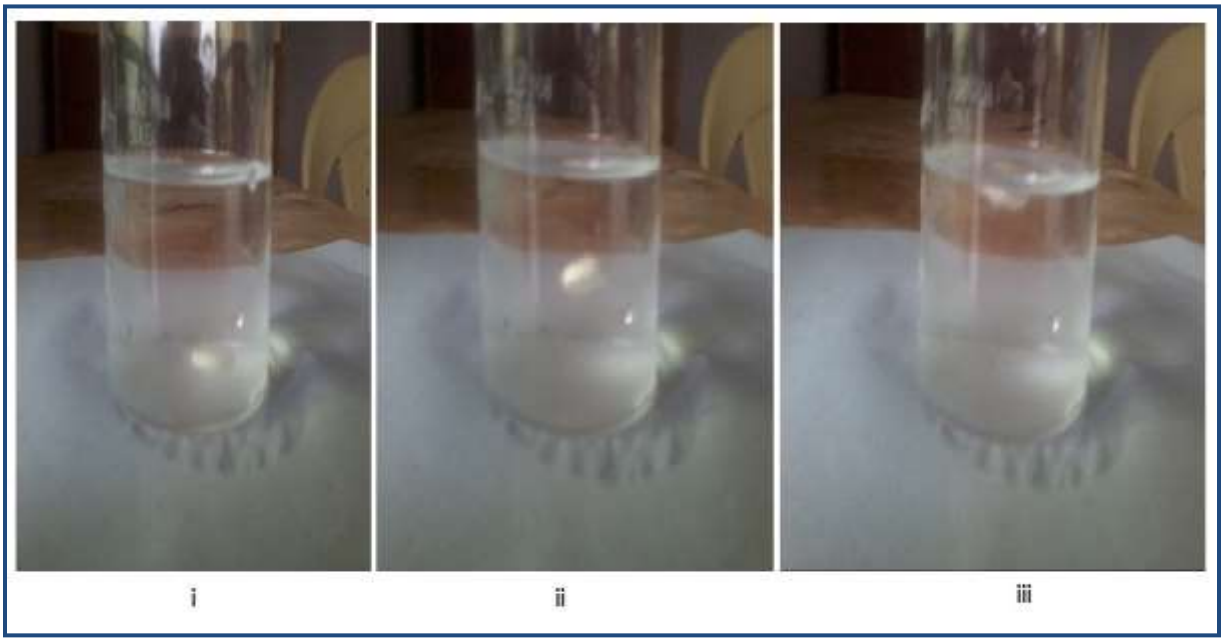

Figure 5: *In vitro* Floating studies of Clopidogrel optimized formulation F4

***In vitro* release data of Clopidogrel from F1-F12 in 0.1N HCl**

In vitro dissolution studies were performed for all the formulations using USP dissolution apparatus II at 50 rpm using 900 ml of o.1N HCl as dissolution medium. The samples withdrawn and were analyzed by using UV spectrophotometer. The drug release from the formulations F1-F3 prepared with HPMC K4M was found to be 100, 93, and 84%, formulations F4-F6 prepared with HPMC K15M was found to be100, 89, 81% show the reasonable drug release, formulation F7-F9 prepared with Xanthan gum 100, 100, 100%, and formulations F10-F12 Prepared with Guar gum 100, 100, 100%. As per the results of dissolution study the formulations F1-F12 the drug release

was sustained for 4 to 12 h. All the formulations were designed as dosage form for 12 h. In order to check the 100% dissolution release profile, formulations were subjected to dissolution studies for 12 h. Among the 12 formulations F4 was best and shows 100% drug release at end of 12 h. It is evident from the *In vitro* dissolution data that increases in HPMC K15M concentration decreases the release rate this might be due to increase in diffusional path length, which the drug molecule may have to travel. So, formulation F4 was selected as the optimized formulation. The results are show in table 10 and figure 6-7

Table 10: *In vitro* release data of Clopidogrel from F1 to F12 in 0.1 N HCL

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	39.00	33.06	16.21	16.94	14.19	13.94	32.61	28.00	25.00	38.00	35.00	31.84
2	50.00	49.18	29.67	26.38	21.34	24.87	45.25	41.00	39.00	65.00	61.00	55.00
4	69.00	58.00	40.00	41.00	37.00	3.60	69.00	64.00	60.00	84.00	79.00	69.00
6	81.00	67.00	50.00	62.00	59.00	48.00	81.00	77.00	76.00	100.00	96.00	81.00
8	96.00	75.00	67.00	81.00	68.00	59.00	94.00	87.00	84.00	100.00	100.00	93.00
10	100.00	86.00	78.00	94.00	77.00	69.00	100.00	99.00	98.00	100.00	100.00	100.00
12	100.00	93.00	84.00	100.00	89.00	81.00	100.00	100.00	100.00	100.00	100.00	100.00

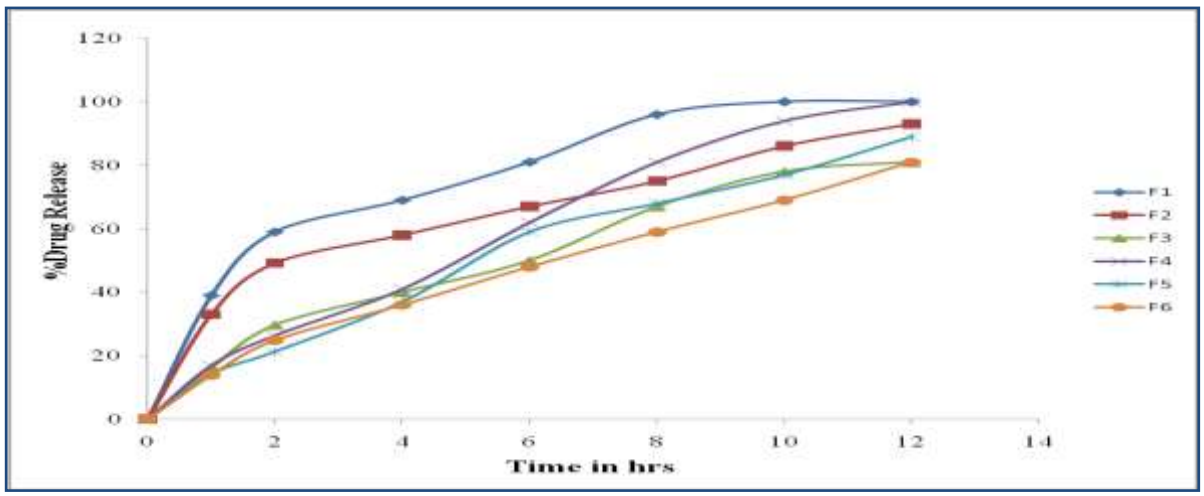

Figure 6: *In vitro* cumulative percentage drug release data of Clopidogrel from F1 - F6 in 0.1N HCl

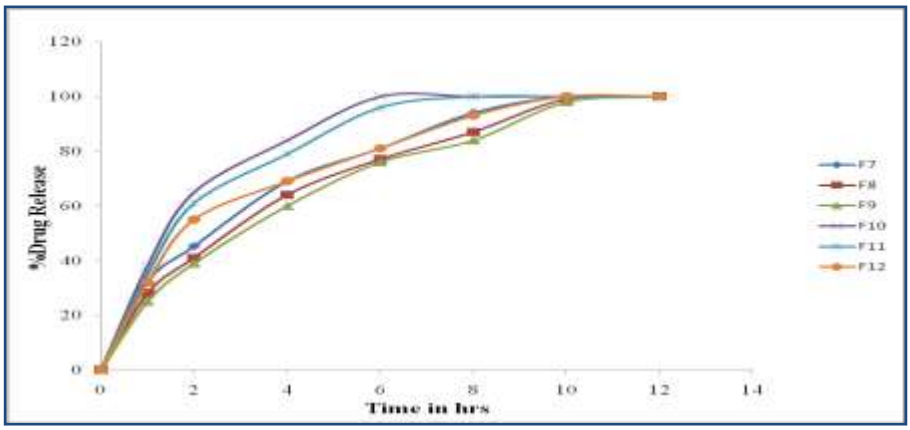

Figure 7: *In vitro* cumulative percentage drug release of Clopidogrel from F7 - F12 in 0.1N HCl

Release kinetics

The *in- vitro* drug release data of the floating tablets were evaluated kinetically by various release models. The regression coefficient (R^2) value for Zero order, First order, Higuchi's, and Peppa's plot for optimized formulation F4 was found to be 0.983, 0.912, 0.982, 0.987. The optimized formulation F4 follows Higuchi's plot since the regression coefficient is 0.982 also plots were found to be linear, which indicates that the drug release depended on the square root of the time and predominantly controlled by diffusion process. The results were presented in table 11. The mechanism of drug release is predicted by using korsmeyer-Peppas equation. The 'n' value of optimised formulation F4 is 0.753 respectively and is between "0.45 to 0.85". This indicates that the drug release depends on swelling, diffusion, and erosion. All formulations follow the non-fickian/anomalous type of diffusion.

Table 11: Release kinetics data of Clopidogrel from F1 –F12 floating tablets

Formulation Code	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Peppa's	
				(R^2)	'n'
F1	0.917	0.908	0.975	0.983	0.409
F2	0.968	0.947	0.985	0.984	0.395
F3	0.983	0.976	0.984	0.992	0.655
F4	0.983	0.912	0.982	0.987	0.753
F5	0.980	0.963	0.986	0.978	0.768
F6	0.994	0.967	0.988	0.992	0.690
F7	0.904	0.961	0.972	0.926	0.525
F8	0.936	0.863	0.987	0.930	0.578
F9	0.945	0.864	0.989	0.905	0.619
F10	0.702	0.990	0.830	0.876	0.492
F11	0.759	0.954	0.875	0.895	0.467
F12	0.895	0.965	0.963	0.909	0.497

Stability studies: Stability studies were carried out on selected formulation (F4) as per ICH guidelines. The results are show in table 12. There was not much variation in matrix integrity of the tablet at all the temperature conditions. There were no significant changes in drug content, physical stability, hardness, friability, drug release, floating lag release, for the selected formulation F4 after 90 days at $40^0C \pm 2^0C/75\%R \pm 5\%RH$.

Table 12: Stability studies of optimized formulation F4 floating tablet

Time (days)	$40^0C \pm 2^0C/75\%R \pm 5\%RH$			
	Hardness (kg/cm^2)	Drug content (%)	% Drug Release	Total floating time
30	4.53	100.5	100	>12
60	4.53	99.89	99.69	>12
90	4.48	99.56	98.99	>12

CONCLUSION

Floating Drug Delivery System are retained in the stomach for a longer time and assist in improving the oral controlled delivery of drugs that have an absorption window in the particular region of the GI tract as well as for controlling the release of the drug having site-specific absorption limitation. Floating Tablets of Clopidogrel are formulated to increase gastric residence time and thereby improve its therapeutic efficacy. The analytical studies, absorbance maxima conforms the drug is pure and not degraded. The compatibility between drug and polymers were studied by using FTIR studies. The results depicts drug and polymer show no significant interaction between them. Higher the viscosities grade of the HPMC, greater the retarding rate of model drug and the order of Controlled release is: HPMC K15M >HPMC K4M respectively. The higher viscosity grade polymer better sustained Clopidogrel drug release. Synthetic polymers was showing more rate retarding drug release and matrix integrity, the order of better controlled release polymers are HPMC K15M >HPMC K4M>xanthum gum>guar gum. When drug : polymer concentration increases the release rate decreases this is because of reason when the concentration of polymer increases the diffusion path length increases. The powder was subjected to pre-compression evaluation such as angle of repose, bulk density, tapped density and compressibility index. It was concluded that powder exhibited good compressibility and flow properties. Formulated tablets showed satisfactory results for various Post compression evaluation parameters like: tablet thickness, hardness, weight variation, floating lag time, total floating time, content uniformity and *In vitro* drug release. Formulation F4 gave better-controlled drug release and floating properties in comparison to the other formulations. The release pattern of the F4 formulation was best fitted to Korsmeyer Peppas model, Higuchi and first-order model.

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