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Research Article

Design and Evaluation of Gastroretentive Multiple Units of Dipyridamole: *in-vitro* and *in-vivo* human studies

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Abstract

Objective: The pH dependent solubility of Dipyridamole was made to select as a model drug for the formulation of gastroretentive drug delivery system. Dipyridamole is highly soluble in acidic pH and as the pH increases the solubility of the drug decreases. The study was planned to formulate, characterize with *in-vitro* and *in-vivo* evaluation in human volunteers.

Method: In this study floating mini matrix tablets of Dipyridamole was formulated using HPMC grade polymers by wet granulation method and prepared multiple units equivalent to one dose were filled in one 000 size empty gelatin capsule. The prepared multiple units were subjected to physical evaluation, *in-vitro* drug release, and stability studies as per ICH guidelines. The *in-vivo* radiographic studies were conducted for determining the residence time of dosage form in human subjects.

Results: All the prepared batches showed good physical properties and *in-vitro* buoyancy. The optimized FD7 formulation remained buoyant for more than 12 h with drug release of more than 90% in 12 h. The drug release kinetics for optimized formulation FD7 followed a first order kinetics with non fickian mechanism. Formulation FD7 was selected as the best formulation based on the *in-vitro* characteristics and subjected for stability and *in-vivo* radiographic studies. These studies revealed that the multiple units were stable during the stability period and remained in the stomach for upto 6 h in human subjects.

Conclusion: Based on *in-vitro* characteristics and *in-vivo* radiographic studies, formulation FD7 was concluded as the best formulation among others. Due to increase in gastric retention time, by choosing floating mini matrix tablets we can improve patient compliance and ensure better disease management.

Keywords: Dipyridamole, Mini matrix tablets, *In-vitro* buoyancy, Stability studies Radiographic Studies,

INTRODUCTION:

Gastroretentive drug delivery systems are retained in the stomach for an extended time period by insisting both spatial and time controlled drug release at a controlled rate. The incorporated drug is released at a predetermined rate continuously and becomes available at the absorption site either in the stomach or upper intestinal tract.[1,2] The gastro retentive dosage form (GRDF) causes increased contact time for the drug with the GI mucosa in the upper GIT, leading to higher absorption, and hence increased therapeutic efficacy, reduction of time intervals for administering the drug, potential reduction of size and dose thus enhanced patient compliance. [3,4]

Dipyridamole is a coronary vasodilator which also inhibits platelet aggregation. The MOA for this drug is that it inhibits both phosphodiesterase and adenosinedeaminase, preventing the degradation of cyclic AMP, an inhibitor in the platelet function.[5,6]

Dose dumping of certain drugs in plasma results inside effects or a reduction in drug concentration at receptor site so an attempt has been made to develop multiple units of Dipyridamole to overcome the problems of dose dumping which is associated with the single unit systems. The multiple units of Dipyridamole were formulated to overcome the all or none drug release associated with single unit gastroretentive systems.[7,8] The intention of developing multiple unit dosage forms is to develop a formulation that has all the advantages of a single unit dosage forms and devoid of dose dumping. The formulated multiple units either can be compressed again as a single tablet which upon disintegration liberates the individual units or these multiple units can be filled into the gelatin or HPMC capsules.[9] The aim of the study is to formulate and evaluate the gastroretentive multiple units of Dipyridamole and to prove its retention in *in-vivo* condition in human subjects. This investigation further requires establishing the pharmacokinetics of the drug in human volunteers by performing bioavailability studies.

MATERIALS AND METHODS

Materials:

Dipyridamole was obtained as a gift sample from AET Laboratories, Hyderabad, Telangana. Hydroxy Propyl Methyl Cellulose (HPMC) K_4M, HPMC $K_{15}M$, HPMC $K_{100}M$ was obtained as a gift sample from Signet Chemical Corporation, Mumbai. Micro crystalline cellulose PH102, Concentrated Hydrochloric acid, Magnesium stearates, talc, Isopropyl alcohol and Polyvinylpyrrolidone (PVP) K 30 were procured from local suppliers.

Methods:

Formulation of Multiple unit floating effervescent Tablets of Dipyridamole:

The multiple unit floating effervescent tablets of this research work are prepared by wet granulation method. In a mortar the drug along with all the excipients like polymers HPMC K_4M, HPMC $K_{15}M$, HPMC $K_{100}M$,sodium bicarbonate, lactose anhydrous are mixed and then the non aqueous granulation is carried out by using 10 % of PVP in isopropyl alcohol solution. Wet mass was passed through 10 mesh and wet granules were dried at 50 - 60°C for 30 min in tray drier. Dried granules were passed through the 18 mesh. Magnesium stearate and talc were added to granules and mixed well in a polybag for 5 minutes. The compression of final blend was carried into mini tablets by using 4mm size round multitip concave punches and corresponding dies on 16 station rotary compression machine (Cemach, India).

Table 1: Tablet Composition of Multiple Unit Floating Matrix Tablets of Dipyridamole

Code	Dipyridamole (mg)	HPMC K_4M (mg)	HPMC $K_{15}M$ (mg)	HPMC $K_{100}M$ (mg)	$NaHCO_3$ (mg)	Lactose Anhydrous (mg)	Mg. Stearate (mg)	Talc(mg)
FD1	5	10	_	_	2.5	31	0.5	1
FD2	5	15	_	_	2.5	26	0.5	1
FD3	5	20	_	_	2.5	21	0.5	1
FD4	5	25	_	_	2.5	16	0.5	1
FD5	5	_	10	_	2.5	31	0.5	1
FD6	5	_	15	_	2.5	26	0.5	1
FD7	5	_	20	_	2.5	21	0.5	1
FD8	5	_	25	_	2.5	16	0.5	1
FD9	5	_	_	10	2.5	31	0.5	1
FD10	5			15	2.5	26	0.5	1
FD11	5			20	2.5	21	0.5	1
FD12	5			25	2.5	16	0.5	1

Total weight of one mini tablet = 50mg

10 mini tablets were filled in one 000 size gelatin capsule

Construction of Calibration Curves

Standard graph of Dipyridamole in 0.1N HCl

Dipyridamole stock solution was prepared by transferring 100 mg of Dipyridamole into 50mL of 0.1 N HCl contained in a 100 mL volumetric flask. 0.1 N HCl was gradually added and made up to the mark with 0.1 N HCl. Necessary dilutions were made from the stock solution to give the concentrations ranging from 0 -15µg/mL. Absorbance's of each test solution was measured at λ max of 284nm using UV -visible spectrophotometer against 0.1N HCl considering as blank and plotted graphically to give the standard graph of dipyridamole. Similarly the standard graphs in different media such as pH 4.5 acetate buffers, pH 6.8 phosphate buffer and pH 7.4 phosphate buffers were prepared. [10,11]

Solubility Study of Dipyridamole:

Excess amount of Dipyridamole was placed in 0.1N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8 and phosphate buffer pH 7.4 respectively in order to determine its solubility. The samples were shaken for 24h at 37±0.1ºC in a horizontal shaker. The supernatant was filtered and the filtrate was diluted with the respective medium and assayed by UV/Visible spectrophotometer at 284nm. [12]

Drug-Excipient Compatibility Studies:

Fourier Transform Infrared (FTIR) Spectroscopy

Infrared spectra were taken by KBr pellet technique using a Bruker Alpha FTIR Spectrophotometer from 400 to 4000 cm−1 wavelength region. The procedure consisted of dispersing a sample (drug alone and optimized formulation of drug) in KBr and compressing into discs by applying a pressure of 5 tons. The FTIR spectra of samples were obtained using FTIR spectroscopy.

Evaluation of Final Blend:

The pre compression properties which are useful in determining the type of formulation methodology to be adopted either granulation or direct compression are angle of repose (determined by fixed funnel method), bulk density and true density (by bulk density apparatus), Carr's index and Hausner's ratio were performed. [12]

Evaluation of physical parameters of multiple unit floating tablets of dipyradimole:

Weight variation test

The weight variation test was carried out by taking 20 tablets randomly from each batch. Each tablet weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight, and the percentage deviation for each tablet was calculated using the following formula: [13,14]

% Deviation = (Individual tablet weight – Average weight of 20 tablets/Average weight of 20 tablets) × 100

Thickness test

Thickness of the tablets was determined by screw gauge. Five tablets were taken and their thickness was recorded and the average thickness along with the standard deviation is reported. [15,16]

Hardness test

The hardness of tablets was determined using Monsanto hardness tester. The hardness of 10 tablets was determined and the average is calculated and reported with the standard deviation. Hardness of the tablet is the force applied across the diameter of the tablet to break the tablet. [17,18]

Friability test

From each batch, 20 tablets were selected randomly and weighed. In the Roche friabilator, each group of tablets was rotated at 25 rpm for 4 min (100 rotations). To determine the loss in weight the tablets were then dedusted and reweighed. Friability was then calculated as per weight loss from the original tablets. [19,20]

% Friability = [(W1 – W2)/W1] × 100

Where, W1 = Initial weight of 20 tablets,

W2 = Weight of the 20 tablets after testing.

Drug content

About 20 tablets were taken, powdered and the powder equivalent to one dose was transferred to a 100 mL volumetric flask and 0.1 N HCl was added. The volume was then made up to the mark with 0.1 N HCl. The solution was filtered and diluted suitably, and drug content in the samples was estimated using ultraviolet (UV)-visible spectrophotometer at λ max 284 nm. [21]

***In vitro* buoyancy studies**

The *in-vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et al*., 1994.[22] The tablets were placed in a 200 mL beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and to float was determined as floating lag time. The duration of time for which the dosage form constantly remained on the surface of medium was determined as the total floating time.

***In -Vitro* Drug Release Characteristics:**

The *in-vitro* drug release study was performed for all the formulations using USP Type II dissolution apparatus under the following conditions.

Dissolution test parameters

Dissolution media: 900mL of 01.N HCl.

Rotational Speed: 50 rpm

Temperature: (37±0.1ºC)

Sampling volume: 5ml

Sampling time: 0.5, 1, 2, 3, 4, 6, 8, 10, 12 h

At predetermined time intervals, 5 mL of samples were collected and replenished with the same volume of fresh medium. The drug content in the samples was estimated using UV-Visible spectrophotometer at a λ max of 284 nm.

Stability Studies:

The stability of the optimized formulations was studied for six months as per the guidelines of ICH. After storage, the optimized formulations were subjected to a drug assay, buoyancy behavior and *in-vitro* drug release [23-24].

Determination of *In-Vivo* Gastric Residence Time in human volunteers

The X-ray studies (*In-vivo)* were approved by the institutional ethical committee with approval No.IHEC/VGOPC/0592015. Multiple units were administered to healthy human volunteers aged 20-25 years and weighing 50-60kgs were selected for these studies. For these studies, optimized floating formulation FD7 was modified by replacing Dipyridamole with X-ray grade barium sulfate which is a radio-opaque substance, keeping all other ingredients constant. The *in-vivo* gastric residence time determination was carried out in fed conditions. In fed state, the tablet was administered to the volunteer after taking a standard fat and Protein meal and for every half an hour 200mL of water was administered to the volunteers to help the tablet to float in the gastrointestinal contents [25-26].

RESULTS

Calibration curves of dipyridamole:

UV-Spectro-photometric method was used for the estimation of Dipyridamole. A solution of Dipyridamole (10µg/mL) was scanned in the wavelength range of 200-400 nm and found to have maximum absorption (λ_{max}) at 284 nm. The standard plots of Dipyridamole were prepared in 0.1 N HCl (pH 1.2) and, pH 4.5 Acetate buffer, Phosphate buffer pH 6.8 and in Phosphate buffer pH 7.4. The standard graphs showed good linearity with R^2 values ranging from 0.9990 to 0.9996.

Solubility Study of Dipyridamole:

The solubility of Dipyridamole in different buffers is shown in Table 5.2.2 & Figure 5.2.5. Dipyridamole is soluble in 0.1N HCl (45.24 mg/mL). With increase in pH solubility was decreased. The solubility's of dipyridamole were found to be for different medias such as pH 4.5 solubility (20.22 mg/mL), pH 6.8 solubility (2.4 mg/mL), pH 7.4 solubility (1.6 mg/mL).

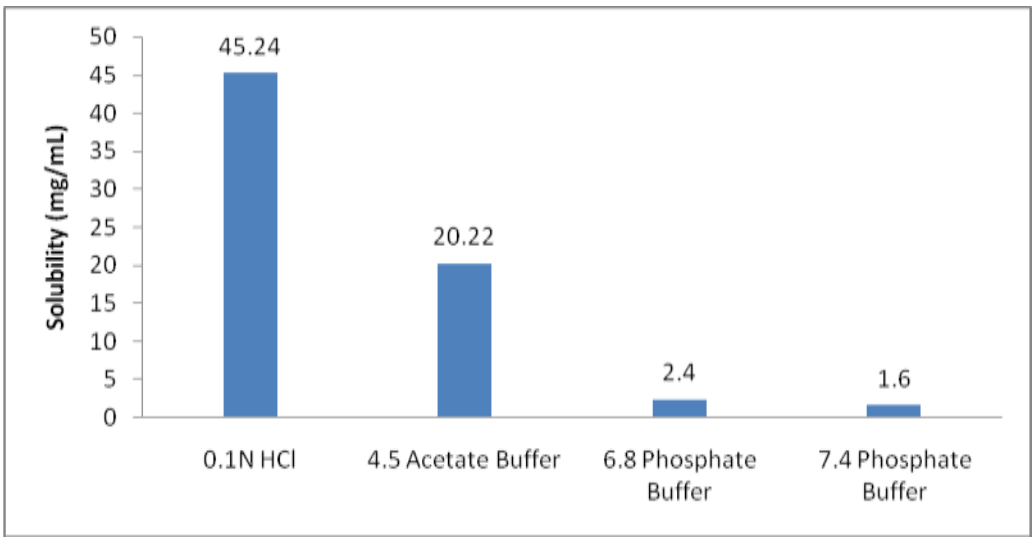


Figure 1: Solubility study data of Dipyridamole

Drug-excipients compatibility studies:

The thermal behaviour of pure drug and optimized formulation is compared in the FTIR spectrum.The FTIR studies confirmed that there are no drug polymer interactions. The result indicated the absence of interaction because the major functional group peaks which were present in the pure dipyridamole were also present in the optimized formulation without much variation in the peak values. It presumably suggests that the dipyridamole molecule is present in an unchanged state in the formulation.

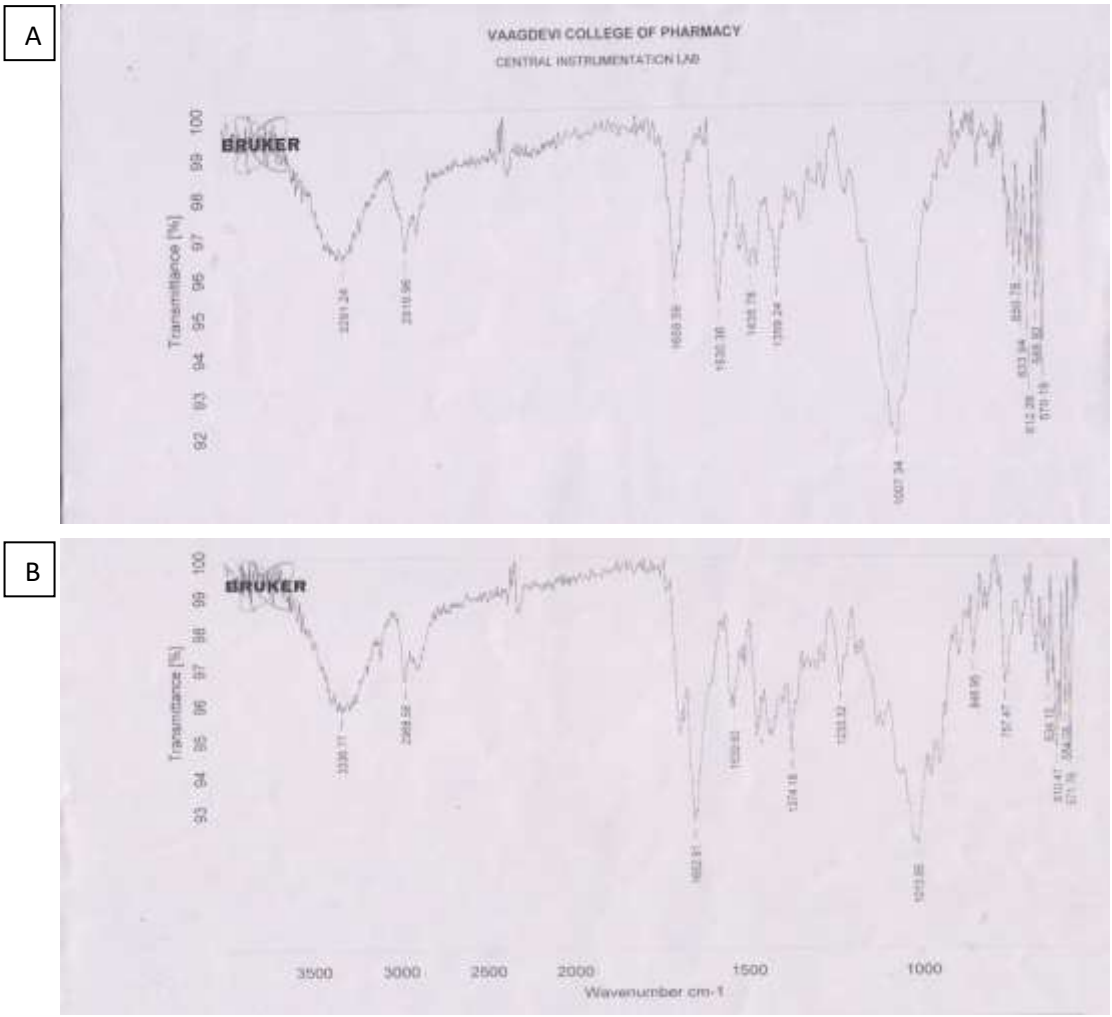


Figure 2: A. FT-IR spectrum of pure Dipyridamole and B. optimized formulation of Dipyridamole

Evaluation of Physicochemical Parameters of Multiple Unit Floating Matrix Tablets of Dipyridamole

All the prepared formulations of multiple unit tablets were tested for Physical evaluations like hardness, thickness, friability and weight variation and these parameters were found to be within the Pharmacopeial limits. The assay of all the formulations was also found to be within the acceptable limits.

Table 2: Physicochemical parameters of multiple unit floating tablets of Dipyridamole

Formulation code	Weight variation Mean ± SD (n=20)	Hardness (kg/cm^2) Mean ± SD (n=10)	Thickness (mm) Mean ± SD (n=5)	Friability (%) (n=20)	Assay (%) Mean ± SD (n=3)
FD1	50.09±1.19	5.1±0.55	3.59±0.05	0.41	99.72±1.36
FD2	48.65±2.27	4.6±0.25	3.47±0.25	0.23	101.45±2.24
FD3	52.15±3.84	5.4±0.50	3.96±0.04	0.29	99.73±1.24
FD4	52.23±1.45	5.2±0.48	3.42±0.12	0.32	98.44±1.16
FD5	49.05±4.12	5.0±0.54	3.71±0.05	0.12	100.85±1.48
FD6	50.60±2.43	4.9±0.35	3.68±0.13	0.16	101.13±2.14
FD7	50.31±0.97	4.8±0.30	3.78±0.05	0.32	99.23±1.42
FD8	48.08±0.19	5.4±0.54	3.30±0.06	0.19	99.83±1.68
FD9	52.80±2.32	4.8±0.48	3.45±0.13	0.26	98.65±1.12
FD10	48.09±1.71	5.4±0.35	3.97±0.04	0.33	100.85±2.24
FD11	49.05±2.53	5.2±0.26	3.86±0.16	0.24	100.12±2.18
FD12	49.37±2.32	4.9±0.40	3.87±0.06	0.29	99.64±2.05

SD=Standard deviation

Floating Properties of Multiple Unit Floating Matrix Tablets of Dipyridamole

The Total floating time and floating lag time for all the formulations were tested. All the formulations exhibited good *in vitro* buoyancy. The floating lag time was found to be in the range of 55-85 seconds. Total floating time was observed in between 6 to 12 hours. The results of the *in vitro* buoyancy study are shown in the Table 3.

Table 3: Floating properties of multiple unit matrix tablets

Formulation code	Floating Lag time (seconds) Mean ± SD (n=3)	Total floating time (hours)
FD1	76±2.48	6
FD2	82±3.32	8
FD3	63±2.46	>12
FD4	68±2.73	>12
FD5	69±2.37	8
FD6	72±2.34	9
FD7	55±3.16	>12
FD8	85±2.44	>12
FD9	76±3.18	>12
FD10	83±2.25	>12
FD11	84±2.30	>12
FD12	78±2.81	>12

***In-vitro* drug release of multiple unit floating matrix tablets of Dipyridamole:**

Formulation FD1 showed rapid burst release within 6 hours. FD2 released more than 90% of the drug within 8 hours which may be due to utilization of less quantity of polymer in the formulation which lead to loss of integrity of the tablets. Formulation FD3 sustained the drug release up to 12 hours and released more than 90% where as FD4 formulation was unable to release the drug completely up to 12 hours.

Formulation FD5 & FD6 released more than 90% of the drug within in 8 hours. Formulations FD7 released more than 90% of the drug and sustained the drug release up to 12 hours. Formulation FD8 was unable to release the drug completely within 12 hours and sustained for more than 12 hours. Formulations FD9 and FD10 showed the drug release of more than 90% in 12 hours whereas FD11 and FD12 sustained for more than 12 hours and were unable to release the drug completely up to 12 hours.

In the formulation of floating multiple units of dipyridamole the formulation which has shown drug release of more than 90% in 12 hours with minimum floating lag time was considered for optimization. This criterion was satisfied by formulation FD7 and subjected to further evaluation tests for stability and *in-vivo* X-ray studies.

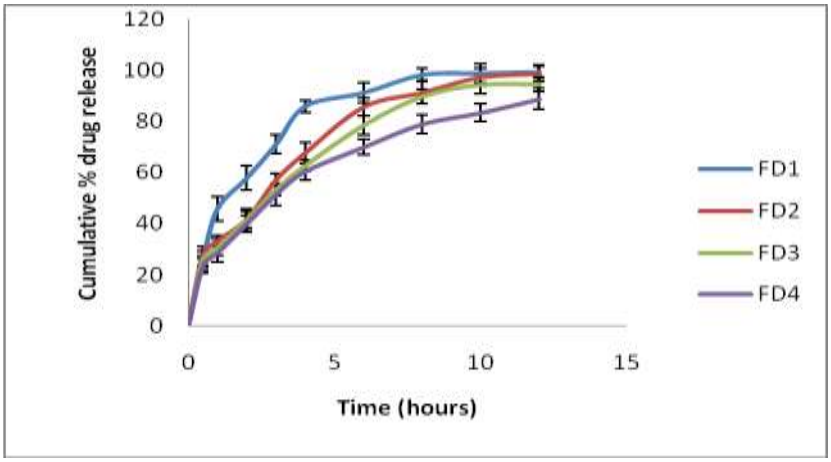


Figure 3: Cumulative % DR of formulations containing HPMC K_4M

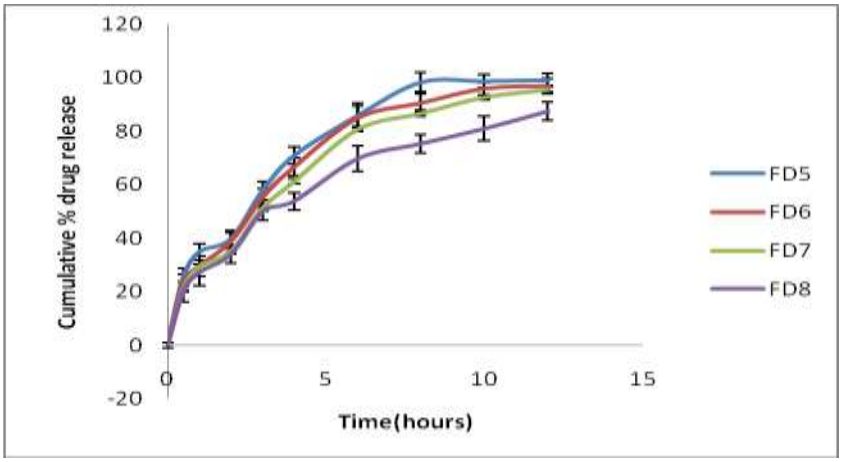


Figure 4: Cumulative % DR of formulations containing $HPMCK_{15}M$

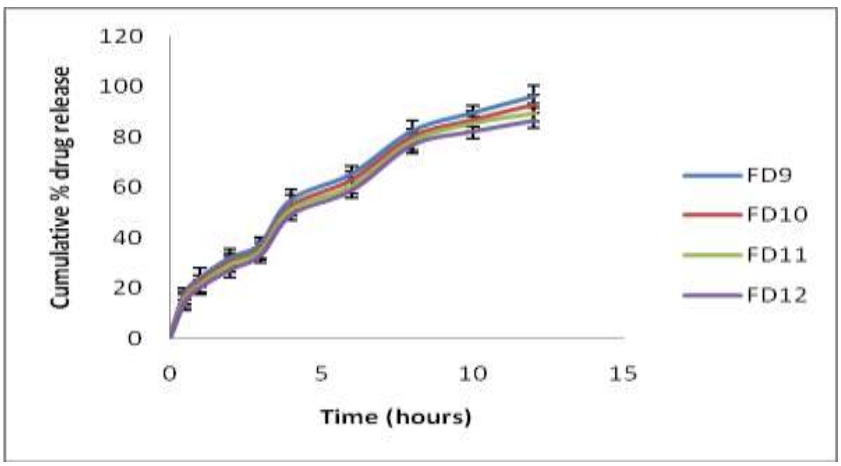


Figure 5: Cumulative % DR of formulations containing $HPMCK_{100}M$

Regression coefficient (r^2) values of floating multiple unit matrix tablets for different kinetic models

The mechanism of drug release for all the formulations FD1 to FD12 followed first order release kinetics which is evident from their R^2 values for first order kinetics(first order r^2> zero order r^2). The Higuchi r^2 values which are nearer to one indicate diffusion mechanism for their drug release. The diffusional exponent (n) values for all the formulations indicate fickian (diffusion controlled) mechanism (n<0.5) except FD7, FD9, FD10, FD11 and FD12 which followed non fickian (diffusion + erosion controlled) mechanism (n>0.5).

Table 4: Regression coefficient (r^2) values of floating multiple unit matrix tablets

Formulation Code	r^2				Peppas (n)
	Zero	First	Higuchi	Korsmeyer & Peppas	
FD1	0.72	0.98	0.92	0.93	0.41
FD2	0.85	0.98	0.97	0.97	0.44
FD3	0.87	0.98	0.98	0.98	0.45
FD4	0.86	0.99	0.98	0.99	0.44
FD5	0.83	0.95	0.96	0.97	0.46
FD6	0.86	0.99	0.97	0.97	0.49
FD7	0.88	0.98	0.97	0.97	0.51
FD8	0.89	0.99	0.99	0.98	0.48
FD9	0.93	0.98	0.98	0.98	0.55
FD10	0.94	0.98	0.98	0.98	0.56
FD11	0.94	0.98	0.98	0.98	0.58
FD12	0.95	0.98	0.97	0.98	0.60

r^2 = Correlation coefficient values, n = Diffusional exponent values

Stability studies

The stability of the optimized formulations was studied for six months as per the guidelines of ICH. After storage, the optimized formulations were subjected to drug assay, buoyancy behavior and *in-vitro* drug release.

Table 5: Stability study of optimized formulation (FD7) for multiple units of Dipyridamole

Parameters observed during stability study	0 month	After 3 month	After 6 month
Assay % mean±SD (n=3)	99.23±1.42	98.46±1.68	99.16±1.37
Floating lag time (Seconds) mean±SD (n=3)	55±3.16	57±2.12	56±1.82
Total floating time (hours) mean±SD (n=3)	>12	>12	>12

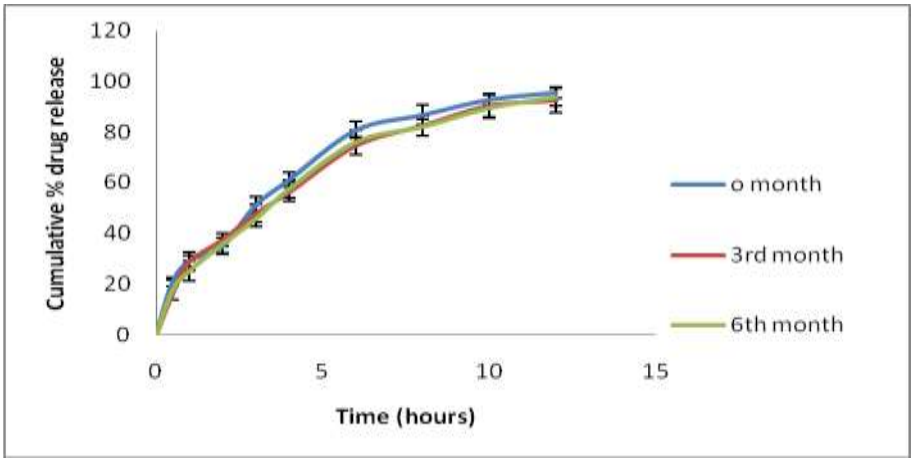


Figure 6: Cumulative % DR of optimized formulation FD7 at 0, 3rd and 6th month.

The dissolution data of optimized formulation FD7 showed, no significant changes (f_2 value was more than 50 i.e 71.02 at 3rd month and 71.26 at 6th month and f_1 value less than 15 i.e 5.70 at 3rd month and 5.76 at 6th month) which indicate good similarity between dissolution profiles during stability period. The assay % and floating parameters after the stability period has not shown much variations indicating good physical stability.

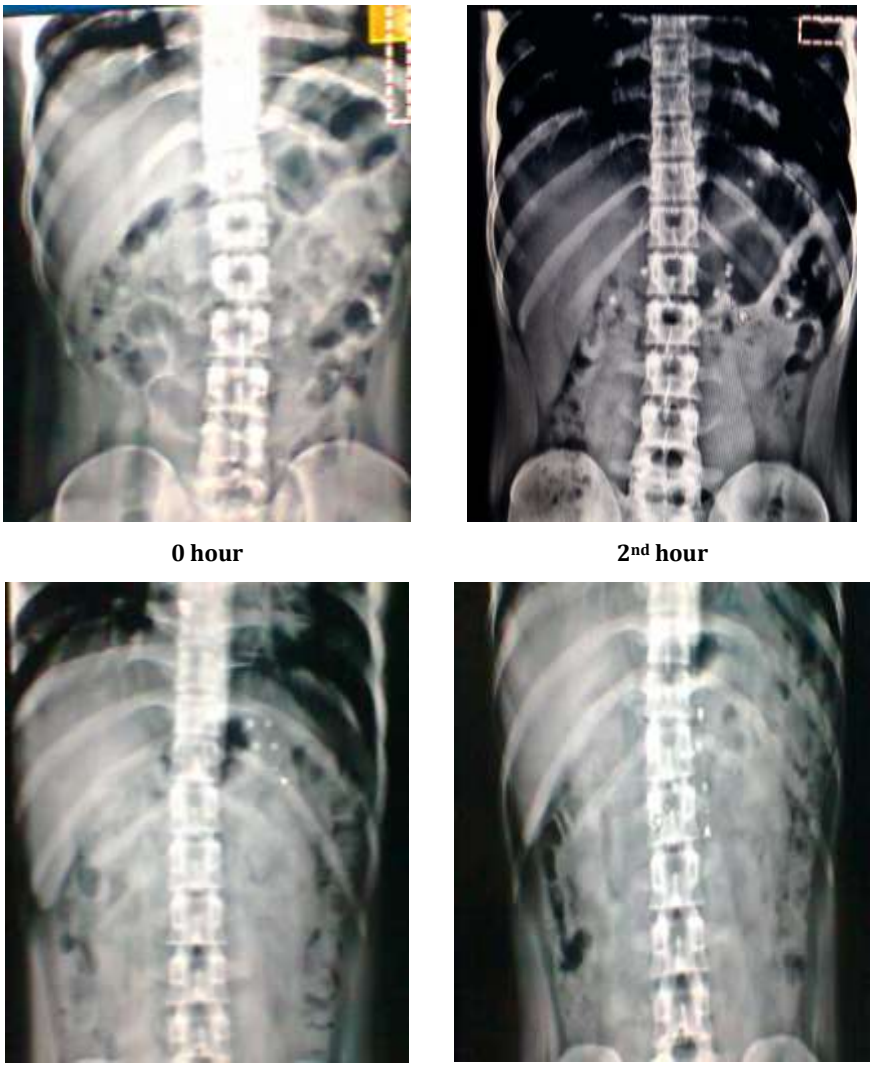
***In-Vivo* X-Ray Studies:**

***In-Vivo* X-Ray Studies for floating multiple units of Dipyridamole.**

Table 6: The Prepared Barium Sulfate loaded multiple units were evaluated for the following parameters:

Parameters	Optimized batch (FD7)	Tablets containing $BaSo_4$
Hardness (Kg/cm^2) mean±SD (n=10)	4.8±0.30	4.8±0.32
Thickness (mm) mean±SD (n=5)	4.78±0.05	4.7±0.02
Floating lag time (Seconds) mean±SD (n=3)	55±3.16	128±3.64
Total Floating time (Hours)	>12	>12

The analysis showed that the $Baso_4$ loaded tablets were similar to the tablets for *in-vitro* testing i.e., for floating properties and the mechanical strength.



0 hour **2nd hour**

4th hour **6th hour**

Figure 7: Radiographic pictures of human volunteers taken at different time intervals.

The behavior of floating multiple units in the human volunteers was observed by using X-ray technique. The X-ray images were taken at different time intervals after oral administration, the tablets were observed in the human stomach after 0 hour. The next pictures were taken at 2nd hour, 4th hour and 6th hour significant changes were detected. The tablets had altered their position and did not adhere to the gastric mucosa but, floated over the gastric contents. During the 6th hour when X-ray image was taken only two or three tablets were observed in radiographic image. Hence X- ray studies suggest that optimized floating multiple units could be retained in the stomach for up to 6 hours.

DISCUSSION:

The present research work was carried out with an intention to develop an optimized multiple effervescent floating units of dipyridamole. Earlier, Katakam et al., and several other people worked on dipyridamole due to its maximum solubility in stomach environment compared to lower gastrointestinal tract hence an attempt has been to develop optimized GRDDS for Dipyridamole. HPMC K grade polymers were utilized as drug release controlling agents in the formulation of multiple floating effervescent units. From the solubility studies it was observed that as the pH of media increases the solubility of dipyridamole decreased and maximum solubility was found to be in the 0.1N HCl. Hence the solubility study for dipyridamole proved it as an ideal drug candidate to formulate into a GRRDS.

The compatibility studies between drug and excipients were performed by FTIR spectroscopy which suggested that there is no major shifting of the important functional group peaks indicating the absence of incompatibility between drug and excipients. Physicochemical parameters of all the prepared formulations were evaluated and found to be good and complied with pharmacopeial limits of USP.

The floating characteristics such as FLT and TFT which are one of the important factors to be considered in the optimization of floating systems were determined as per the Rosa et.al method. The formulation which has shown minimum FLT and *in-vitro* TFT of more than 12 hours were considered for optimization. This criterion was satisfied by FD7.

The release of drug from floating units was controlled for an extended period of time due to its viscous nature from the HPMC matrix through which drug diffuses. HPMC K_4M, HPMC $K_{15}M$ and HPMC $K_{100}M$ were used to retard the drug release up to 12 hours, maintaining the integrity and buoyancy of the tablets formed. The rapid drug release from floating tablets with low concentration of polymer may be due to matrix erosion and as the concentration of polymer was increased the drug release from the matrix sustained for desired period of time with diffusional swelling and a slight erosion mechanism in the latter. The drug release (*in-vitro*) from FD7 formulation have shown drug release of more than 90% with minimum floating lag time as compared to other formulations were considered as optimized formulation. Formulation FD7 followed first order kinetics and the r^2 values of Higuchi model which are nearer to one suggested diffusion controlled mechanism for the entire multiple unit formulations. The diffusion exponent "n" values for the optimized formulation were more than 0.5 and suggested non-fickian (diffusion+ erosion) drug release.

Based on *In-vitro* drug release and floating properties an FD7 formulation was selected as optimized formulations. This was subjected to stability studies, *in-vivo* radiographic studies in human volunteers to determine the Gastric retention time.

As per ICH and WHO guidelines the stability studies were performed for the optimized formulation FD7. The critical parameters such as assay, floating characteristics, and drug release (*in-vitro)* were studied during and after the stability period. The results indicated very little variations in the parameters. The similarity factor (f_2) and difference factor (f_1) were also calculated for dissolution data and the values for f_2 factor was more than 50 and f_1 was less than 15 which suggested that the dissolution curves after 3rd month and 6th month are similar to the initial dissolution curve. This indicated that the optimized formulations are stable during their storage period.

In-vivo radiographic studies were conducted for the optimized formulation FD7 and the study proved that the formulated dosage form could be successfully retained in the stomach for upto 6 hours. The multiple units altered its position when the images were taken at different time points which indicated no mucoadhesion with the stomach but floated over the GI contents.

CONCLUSION:

From this research work it is concluded that the adopted methodology successfully developed uniform and reproducible floating multiple units of Dipyridamole with different grades of HPMC polymer exhibiting non fickian first order drug release for the optimized FD7 formulation with good stability during the storage period. In vivo radiographic studies unveiled that optimized formulation can be retained in the stomach upto 6 hours. Based on the research work performed it can be concluded that adopted method can successfully retain the dipyridamole multiple units in the stomach and can release the drug at a controlled rate and released drug can be absorbed from upper part of GIT.

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