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Formulation and Evaluation of Floating Matrix Tablets of Dipyridamole

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ABSTRACT

Single unit floating effervescent matrix tablets of Dipyridamole were successfully prepared with hydrophilic polymers like HPMC K4M , HPMC K15M and HPMC K100M with 10% $NaHCO_3$ by Simple direct compression method with drug: polymer ratio of 1:1.5,1:2,1:2.5:1.3. FT-IR studies were conducted between drug, polymer and various excipients used in the formulations. Evaluation parameters of powder blend like Hausner's ratio, Compressibility index, Angle of repose were carried out and results showed that the powder has good flow properties. Formulated tablets gave satisfactory results for various evaluation parameters like tablet hardness (5-6 Kg/cm^2), weight variation (±10%), Friability (<0.9%), content uniformity (90%-110%), thickness (4-5mm) *in vitro* buoyancy properties and *in vitro* drug release. The floating lag time was found to be less for the formulations FS2, FS5, with 50sec, 48sec, respectively. Even the total floating time was found to be more than 12hrs for FS2, FS5, formulations with more than 90%drug release upto 12hrs. The swelling studies were carried for 24 hrs. The results indicate that the selected polymers were of swellable type and HPMC K4M has marginally more swellability than HPMC K15M and HPMC K100M matrices. In vivo radiographic studies in fed condition the single unit matrix tablets (FS5) showed a gastric residence time of more than 6hrs. Indicated that the tablets remained in the stomach for 6hrs, which indicates the increase in the GRT is due to floating and swelling principle.

Keywords: Dipyridamole, Radiographic Studies, Hydrophilic Polymers, Floating Effervescent Matrix Tablets.

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INTRODUCTION

The oral route currently represents the most predominant and preferable route of drug delivery. Unlike majority of parentral dosage forms, it allows ease of administration by the patient, and therefore a highly convenient way for substances to be introduced into the human body. Oral drug delivery systems have progressed from conventional immediate release to site-specific delivery over a period of time. Every patient would always like to have an ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action. Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms includes

1) Conventional Drug Delivery System[1]

2) Controlled Drug Delivery System [2,3]

Controlled release dosage forms (CRDF) have been developed for over three decades. They have increasingly gained popularity over other dosage forms in treating disease[2]. The goal in designing controlled drug delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery[3]. So controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Concept of absorption window[4]

Drug exhibiting absorption from only a particular portion of GI tract or showing difference in absorption from various regions of GI tract are said to have regional variability in intestinal absorption. Such drugs show absorption window which signifies the regions of GI tract from where absorption primarily occurs. Drug released from the CRDDS after the absorption window has been crossed goes waste with no or negligible absorption occurring. This phenomenon drastically decreases the available drug for absorption, after release of drug from CRDDS. The CRDDS possessing the ability of being retained in the stomach are called GRDDS and they can help in optimizing the oral controlled delivery of drugs having absorption window by continuously

releasing drug prior to absorption window, for prolonged period of time thus ensuring optimal bioavailability.

Gastro-Retentive Drug Delivery Systems[5,6,7]

Gastro-retentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically, gastro-retentive system retains in the stomach for a number of hours and continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance. Therefore, Sustained release DDS possessing gastric retention properties may be potentially useful.

Suitable Drug Candidates For Gastroretention[7]

1. Drugs that have narrow absorption window in GIT
2. Drugs those are locally active in the stomach
3. Drugs those are unstable in the intestinal or colonic environment
4. Drugs that disturb normal colonic microbes
5. Drugs that exhibit low solubility at high pH values

Approaches to Gastric Retention[8,10]

Various approaches have been pursued to increase the retention of oral dosage forms in the stomach. The most common approaches used to increase the gastric residence time of pharmaceutical dosage forms include

- Floating systems
- Swelling and expanding systems
- Bioadhesive systems
- Unfolding and modified- shape systems
- High density systems

MATERIALS AND METHOD

Dipyridamole was gift sample from AET Labs. Hyderabad, HPMC K4M, HPMC K15M and HPMCK100M were obtained from Signet Chemical Corporation, Mumbai, Lactose Mono hydrate, Conc. Hydrochloric acid; Magnesium stearate, Talc and Sodium bicarbonate were procured from local chemical distributors.

Need for the Investigation

Dipyridamole, a non-nitrate coronary vasodilator that also inhibits platelet aggregation, is combined with other anticoagulant drugs, such as warfarin, to prevent thrombosis in patients with valvular or vascular disorders. Dipyridamole is also used in myocardial perfusion imaging, as an antiplatelet agent, and in combination with aspirin for stroke prophylaxis. It can also act as Phosphodiestarase. Dipyridamole is considered a good candidate for incorporation in a gastro retentive dosage form due to its high solubility in the stomach pH comp ared to its solubility in the small intestine pH[60]. As its solubility decreases with increases in pH, it would be more beneficial to retain the drug in stomach (acidic environment) for prolonged duration so has to achieve maximum absorption and bioavailability. So gastro retentive drug delivery system is desirable to prolong the residence time of the dosage form in the stomach or upper gastrointestinal tract untile the drug is completely released from the system.

Formulation Development

Preparation of Single Unit Floating Matrix Tablets of Dipyridamole

Technology Applied: Direct compression.

The key ingredients included in the formulations are:

- Hydrophilic Polymers: HPMC K4M, HPMC K15M and HPMC K100M to modify the pattern of drug release from matrix.
- Effervescent agent: Sodium bicarbonate
- Filler: Lactose Anhydrous
- Antiadherant: Talc
- Lubricant: Magnesium Stearate.

Accurately weighed quantities of polymer and Lactose were taken in a motor and mixed geometrically, to this required quantity of Dipyridamole was added and mixed slightly with pestle. Accurately weighed quantity of sodium bicarbonate was taken separately in a motor and powdered with pestle. The powder is passed through sieve no 40 and mixed with the drug blend which is also passed through sieve no 40.The whole mixture was collected in a plastic bag and mixed for 3 min. To this magnesium stearate was added and mixed for 5min, later Talc was added and mixed for 2min. The powder blend equivalent to 250mg was compressed into tablets with 8mm. flat punches at a hardness of 5-6 kg/cm^2

Composition of Single Unit Floating Matrix

Table 1: Tablets of Dipyridamole

Code	Drug (Dipyridamole)	HPMCK4M	HPMCK15M	HPMC K100M	$NaHCO_3$	Lactose	Talc	Mg.Stearate
FS1	50	75	_	_	25	92.5	5	2.5
FS2	50	100	_	_	25	67.5	5	2.5
FS3	50	125	_	_	25	42.5	5	2.5
FS4	50	150	_	_	25	17.5	5	2.5
FS5	50	_	75	_	25	92.5	5	2.5
FS6	50	_	100	_	25	67.5	5	2.5
FS7	50	_	125	_	25	42.5	5	2.5
FS8	50	_	150	_	25	17.5	5	2.5
FS9	50	_	_	75	25	92.5	5	2.5
FS10	50	_	_	100	25	67.5	5	2.5
FS11	50	_	_	125	25	42.5	5	2.5
FS12	50	_	_	150	25	17.5	5	2.5

Total tablet weight: 250mg, All weights are in mg.

***In – Vitro* Drug Release Data and Profiles**

The dissolution conditions used for studying the drug release from the matrix tablets of DP were:

Apparatus **:** USP Type 2 (paddle)

Agitation speed (rpm) **:** 50

Medium **:** 0.1N HCl (pH 1.2), 900ml

Temperature **:** 37.0 ± 0.5° C

Time **:** 0.5,1, 2, 3, 4, 6, 8, 10, and 12hr

Wavelength **:** 284nm

RESULTS AND DISCUSSION

Solubility of Dipyridamole

The quantitative solubility of DP in different buffers is shown in Table and Figure. DP is highly soluble in 0.1N HCl, having quantitative solubility (45.24 mg/ml). As pH increased solubility decreased drastically, i.e.pH4.5 acetate buffer (20.22 mg/ml), pH 6.8 phosphate buffer(2.4mg/ml),and pH 7.4 phosphate buffer(1.6mg/ml). It shows pH dependent solubility, highly soluble in acidic pH but poorly soluble in alkaline pH.

Table 2: solubility study data of Dipyridamole

Buffer	Absorbance	Dilution factor	Regression Equation	Solubility (mg/ml)
0.1N HCl (pH 1.2)	0.552	500	Y=0.059+0.0151	45.24
pH 4.5 acetate buffer	0.472	100	Y=0.042+0.009	20.22
pH 6.8 Phosphate buffer	0.712	10	Y=0.040+0.002	2.4
pH 7.4 Phosphate buffer	0.623	10	Y=0.036+0.003	1.6

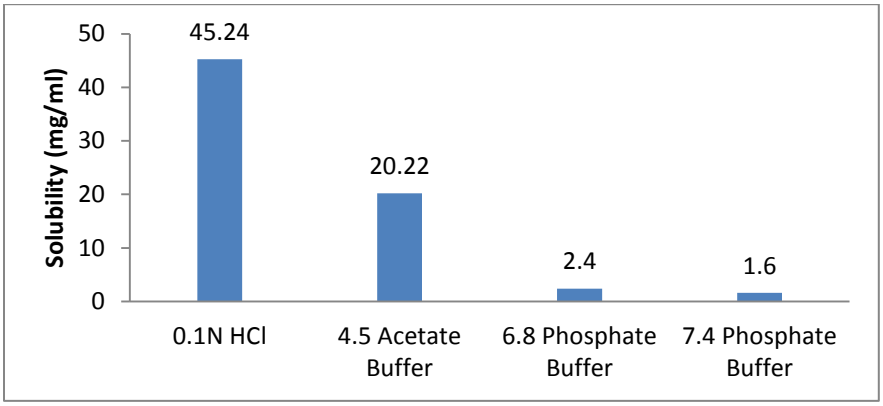


Figure 1: Solubility study data of Dipyridamole

Drug-Excipient Compatibility Studies

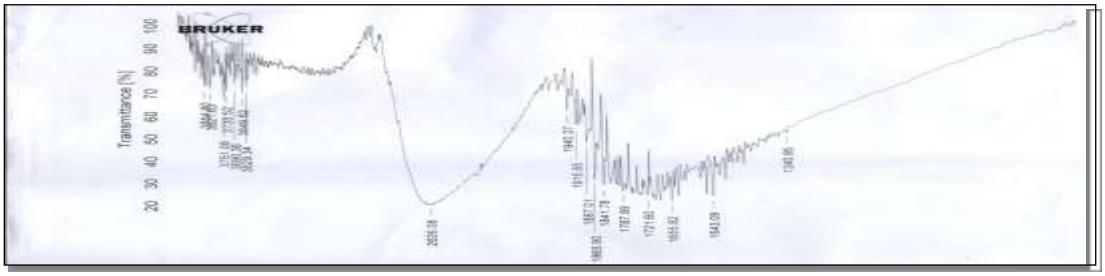
Fourier Transform Infrared (FT-IR) Spectroscopy

Potential chemical interaction between drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibility of chemical interaction between drug and excipients FTIR spectra of pure Dipyridamole and mixture of Dipyridamole, different polymers were analyzed over the range 400 to 4000cm^{-}

Table 3: Functional groups and Range for Dipyridamole and Drug+polymer

Functional group	Absorption range	Pure drug Peak	Drug+HPMC K $_4$M	Drug+HPMC K $_{15}$M	Drug+HPMC K $_{100}$M
Alcohols (O-H)	3650-3580	3648.48	3564.69	3649.62	3649.08
Pyrimidine	1600-1300	1542.22	1542.42	1543.09	1543.13
Alkenes (-C=C-)	2372-2100	2350.89	2371.39	2370.96	2372.63
Aromatic amines	1360-1180	1342.44	1339.57	1340.95	1338.62

(A)



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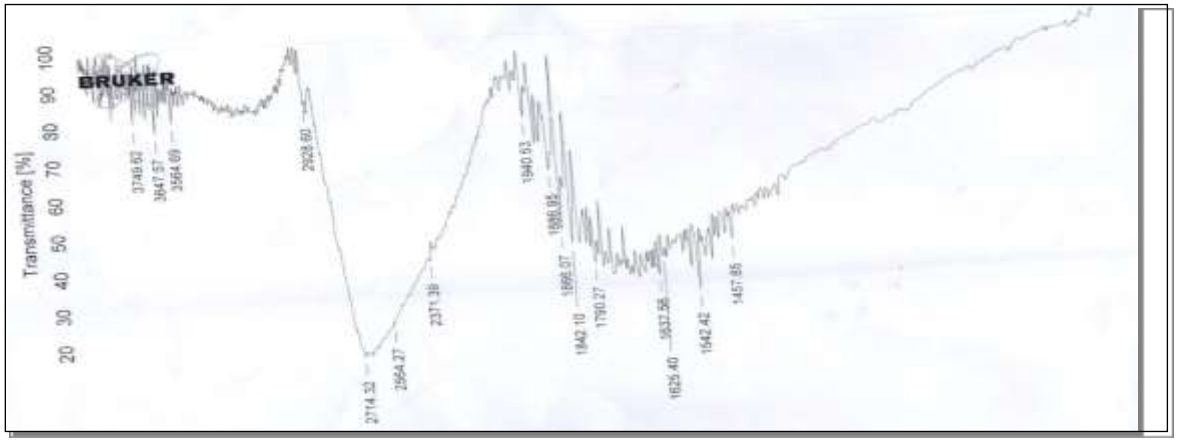

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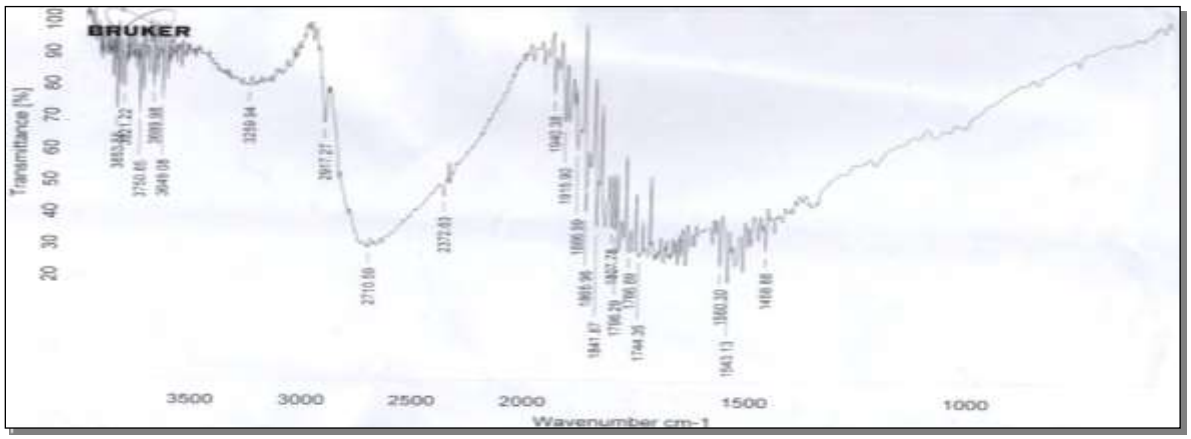


(D)

Figure 2: FTIR spectrum of (a) Dipyridamole (b) Drug+HPMCK4M (c)Drug+HPMCK15M d)DRUG+HPMC K100M Physical Properties of prepared powder blends

The physical properties like Compressibility index (CI), Angle of repose and Hausner ratio were calculated and tabulated.

Table 4: physical properties of powder blends of single unit tablet formulations

Formulation	CI	Angle of repose	Hausner ratio
FS1	12.6	26.8^{o}	1.17
FS2	13.6	27.5^{o}	1.14
FS3	12.5	28.0^{o}	1.13
FS4	15.9	29.4^{o}	1.18
FS5	12.4	28.5^{o}	1.14
FS6	11.2	29.4^{o}	1.13
FS7	15.7	28.4^{o}	1.02
FS8	12.8	26.9^{o}	1.16
FS9	14.6	27.5^{o}	1.15
FS10	11.3	26.8^{o}	1.14
FS11	12.5	27.5 ^{o}	1.16
FS12	12.3	28.0 ^{o}	1.13

The results of the physical tests of many of the blends were in the limits and comply with the standards.

Evaluation of Physical Parameters of Single Unit Floating Matrix Tablets of Dipyridamole

Table 5: Physical parameters of Single unit floating matrix tablets of Dipyridamol

Formulation code	Weight variation(n=20) (mg) ±SD	Hardness (kg/cm^2)±SD (n=6)	Thickness (mm)±SD (n=5)	Friability (%) (n=20)	Assay (%) (%)±SD (n=3)
FS1	250.60±3.84	5.5±0.34	5.38±0.05	0.32	99.23±0.72
FS2	248.33±2.87	5.2±0.54	4.92±0.06	0.19	99.83±0.54
FS3	252.80±2.73	5.4±0.48	5.45±0.03	0.26	98.65±0.62
FS4	248.09±2.13	4.8±0.35	4.97±0.04	0.33	100.85±1.21
FS5	249.05±3.48	5.0±0.26	5.26±0.06	0.24	100.12±1.06
FS6	249.37±2.32	4.9±0.42	4.87±0.06	0.29	99.64±0.22
FS7	250.09±1.19	5.1±0.55	4.59±0.05	0.41	99.72±0.68
FS8	248.65±2.27	4.6±0.25	4.87±0.25	0.23	101.45±2.12
FS9	252.15±3.84	5.4±0.50	4.96±0.04	0.29	99.73±1.05
FS10	252.23±1.45	5.2±0.48	4.48±0.02	0.32	98.44±0.32
FS11	249.05±4.12	4.9±0.54	5.22±0.05	0.12	100.85±1.52
FS12	250.60±2.43	4.9±0.35	4.68±0.03	0.16	101.13±1.84

SD=Standard deviation. The results of the physical tests of many of the formulations were in the limits and comply with the standards.

All the prepared formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeias limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Floating Properties of Single Unit Floating Matrix

Tablets of Dipyridamole

All the formulations were tested for floating properties like floating lag time and total floating time. The results of the tests were tabulated. All the batches showed good *in vitro* buoyancy. The results of the *in vitro* buoyancy study were shown in Tables:

Table 6: Floating properties of single unit matrix tablets

Formulation code	Floating Lag time(sec)	Total floating time (hrs)
FS1	68	8
FS2	50	>12
FS3	58	>12
FS4	70	>12
FS5	48	>12
FS6	57	>12
FS7	78	>12
FS8	98	>12

FS9	60	>12
FS10	71	>12
FS11	79	>12
FS12	94	>12

Release profiles of formulations containing HPMCK4M

Table 7: Cumulative Percentage Drug Release of Formulations with HPMC K4M

Time (hrs)	FS1 (n=3) mean±SD	FS2 (n=3) mean±SD	FS3 (n=3) mean±SD	FS4 (n=3) mean±SD
0	0	0	0	0
0.5	26.32±1.56	8.26±1.92	8.12±2.14	6.14±1.82
1	34.28±2.48	15.23±1.84	14.66±1.28	13.86±2.24
2	56.47±2.94	26.73±2.12	23.26±2.16	22.23±1.26
3	69.66±3.75	38.33±3.25	32.33±2.12	29.86±2.98
4	83.32±2.89	45.12±2.24	44.96±3.26	38.66±2.45
6	94.21±3.46	58.42±2.89	56.28±2.46	45.35±3.48
8	98.57±2.72	76.66±2.48	65.66±1.46	54.23±2.66
10		92.05±3.26	78.26±3.23	69.26±3.91
12		98.12±1.72	85.13±1.48	78.86±2.43

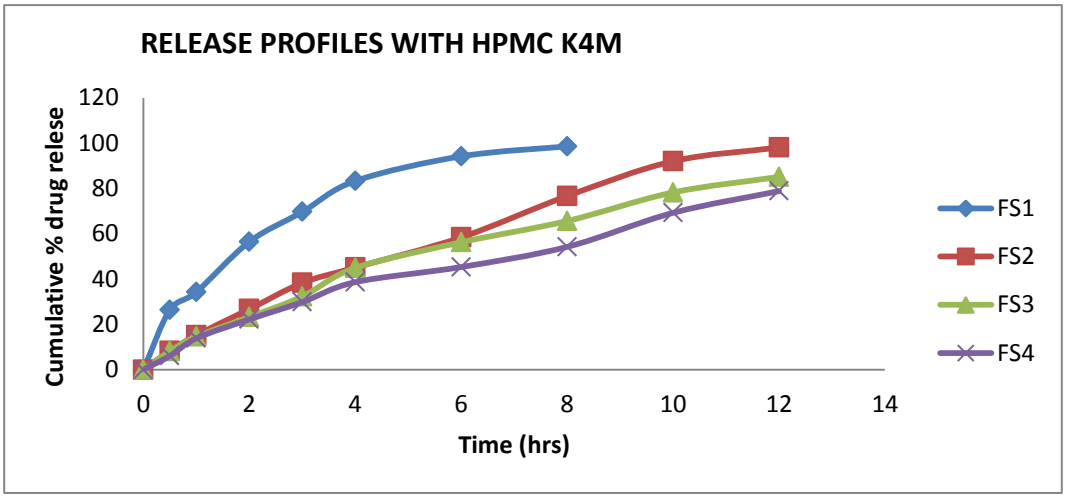


Figure 3: Cumulative% drug release of formulations containing HPMCK4M ii.) Release profiles of formulations containing HPMC $K_{15}M$

Table 8: Cumulative Percentage Drug Release of Formulations with HPMC K15M

Time (hrs)	FS5 (n=3) mean±SD	FS6 (n=3) mean±SD	FS7 (n=3) mean±SD	FS8 (n=3) mean±SD
0	0	0	0	0
0.5	5.92±1.05	5.80±1.12	4.90±1.84	4.61±1.26
1	11.77±1.28	11.54±2.24	10.82±2.25	8.42±2.24
2	20.01±2.48	19.90±2.81	18.21±3.05	15.49±1.62
3	29.78±2.82	26.44±3.16	24.89±3.18	23.66±2.12
4	40.28±3.62	39.05±2.06	33.72±2.94	29.78±1.18
6	58.12±2.38	53.66±2.11	50.18±3.28	46.12±3.65

8	76.42±3.86	69.33±1.92	68.66±3.92	57.26±2.11
10	92.74±3.24	81.26±3.12	74.32±2.06	68.1±3.26
12	99.81±1.68	87.22±1.88	83.12±2.26	77.66±3.94

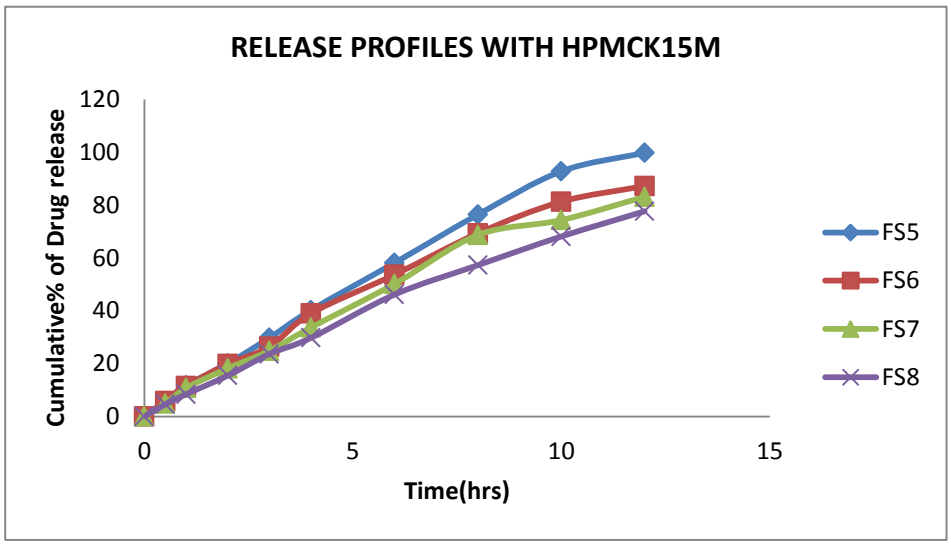


Figure 4: Cumulative% Drug Release of Formulations Containing HPMCK15M iii.) Release profiles of formulations containing HPMC K_{100}M

Table 9: Cumulative Percentage Drug Release of Formulations with HPMC K100M

Time (hrs)	FS9 (n=3) mean±SD	FS10 (n=3) mean±SD	FS11(n=3) mean±SD	FS12(n=3) mean±SD
0	0	0	0	0
0.5	8.45±1.42	6.90±2.12	4.68±1.82	3.71±1.86
1	16.51±2.46	11.66±1.82	9.52±2.34	9.42±1.46
2	24.66±1.56	18.26±3.24	16.11±2.62	14.05±2.68
3	28.27±2.48	21.77±1.62	20.15±1.46	18.77±1.24
4	39.66±1.94	35.15±3.45	29.66±1.32	24.81±2.48
6	48.13±2.72	42.60±2.48	40.15±1.28	31.33±3.12
8	56.21±2.89	53.16±2.79	49.29±2.48	40.41±2.82
10	73.66±3.36	66.09±3.91	55.26±3.22	52.54±1.34
12	80.842.18	74.561.24	67.812.66	59.211.52

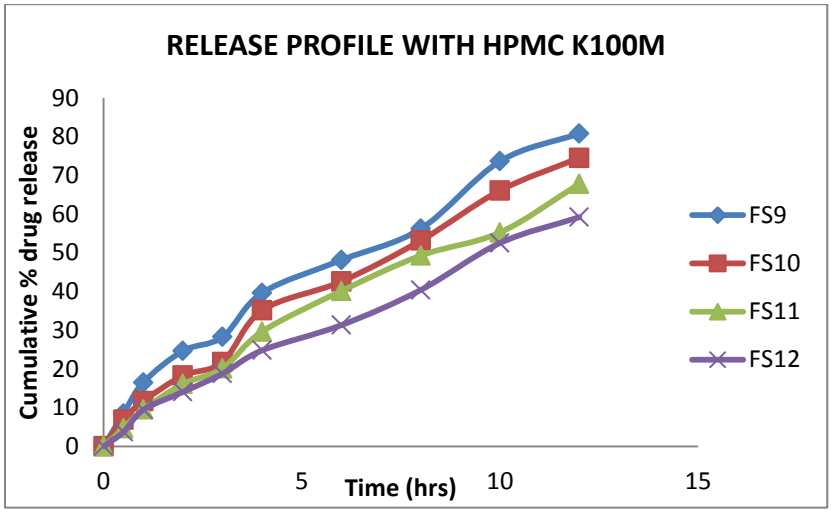


Figure 5: Cumulative% drug release of formulations containing HPMCK100M

Formulation FS1 showed rapid burst release within 7-8hrs. FS1 released within 8hrs only. This is due to the low quantity of polymer used, which resulted in the loss of integrity of the tablet. Formulation FS2 sustained the drug release up to 12hrs. Hence FS2 was considered for optimization formulation. The mechanism of drug release from FS2 was found to be non- fickian diffusion as evident from release exponent (n=0.799) value. FS3 and FS4 released less than 85% and 76% of drug in 12hrs. Formulation FS5 released drug completely in 12hrs. Formulations FS6 FS7 and FS8 released less than 87%, 83% and 77% of drug in 12hrs. The drug released from FS6, FS7, FS8, and FS9 was found to be decreasing order (FS6>FS7>FS8>FS9) due to high level of polymer was used which retard the drug release. FS6 formulation selected as the optimized formulation in HPMCK15 formulation. Drug release from FS5 follows higuchi model. Release exponent (n=0.904) value indicated non- fickian diffusion. Formulations FS9,FS10,FS11 and FS12 showed that drug released as sustained for more than 12hrs.This is because of improper wetting of the matrix as high viscosity grade polymer was used in the preparation of formulation**.** Among FS2 and FS5, the formulation FS5 released more than 90% of the drug within 12 hours and floating lag time was less as compared FS2. So FS5 formulation was considered as optimized formulation and subjected to x- ray studies.

Mathematical Modeling of Dissolution Profiles

Table 10: Regression coefficient (R^2) values of floating matrix tablets for different kinetic models

Formulation	R^2				Peppas(n)
	Zero	First	Higuchi	Korsmeyer &Peppas	
FS5	0.990	0.766	0.981	0.996	0.904

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

Table 11: Swelling Index of HPMC K4M, HPMCK15M and HPMC K100M Polymer tablets

Time (hrs)	HPMC K4M	HPMC K15M	HPMC K100M
0.5	25	18.5	12.5
1	43.75	34.6	25
2	62.5	49.5	37.5
3	87.5	67.25	50
4	100	81.75	62.5
6	106.25	90.5	75
8	112.5	100.5	81.25
10	112.5	100.75	87.5
12	112.5	104.75	93.75
24	-	104.75	106.25

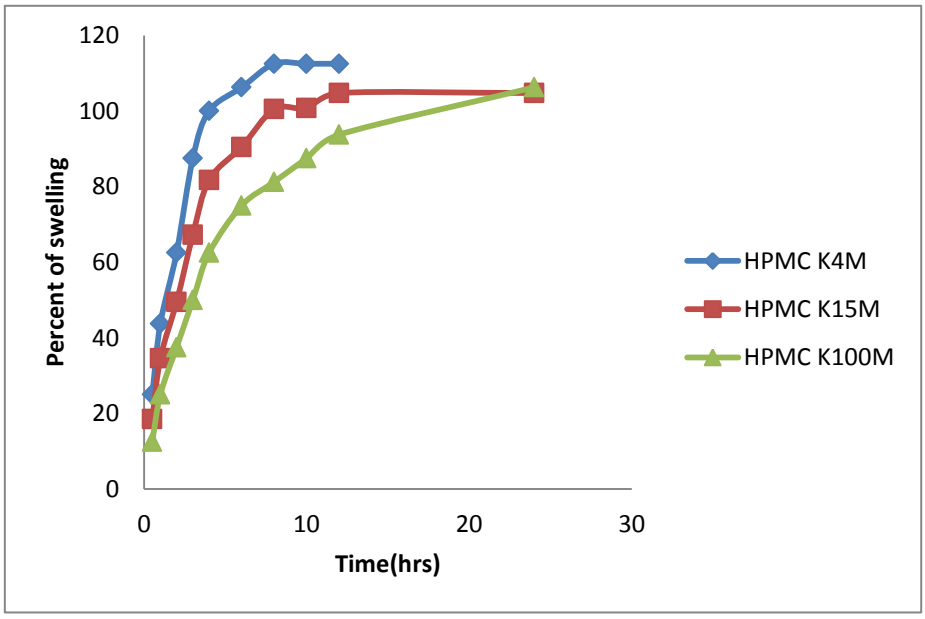


Figure 6: Percent swelling Vs time for HPMC K4M, HPMC K15M and HPMC K100M Polymer tablets

***IN-VIVO* Gastric Residence Time Determination (X-ray Studies)**

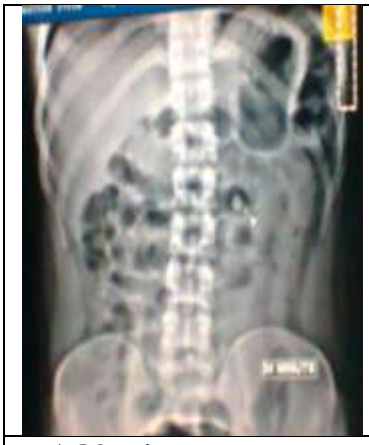
The *In-vivo* X-ray studies were approved by the institutional ethical committee with approval No.IHEC/VGOPC/032/2013.Tablets were administered to healthy human volunteer aged 20-25 years and weighing 50-60kgs were selected for these studies. For these studies, optimized floating formulation FS5 was modified by replacing 30 mg of 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 volunteer to help the tablet to float in the G.I contents.

Table 12: Formula for I*N-VIVO* Radiological Study

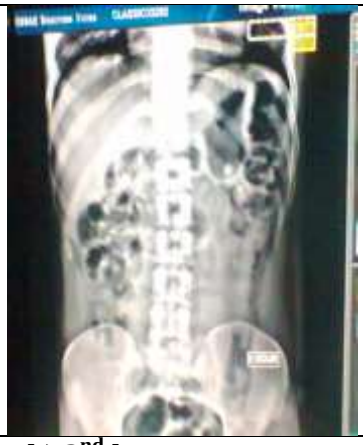
Ingredients	Weight (mg)
Dipyridamole	20
HPMC K15M	75
$BaSO_4$	30
Sod.bi.Carbonate	25
Lactose	94
Mg.Stearate	2
Talc	4
Total Weight	250

Table 13: Prepared Barium Sulfate Loaded Tablets were Evaluated for the Following Parameters

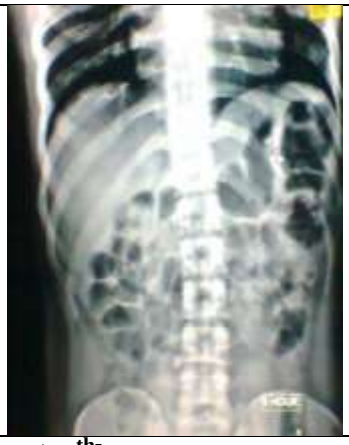
Parameters	Optimized batch	Tablets Containing $Baso_4$
Hardness	5.0±0.26	5.2±0.32
Thickness	5.26±0.06	4.97±0.02
Floating lag time	48 Sec	3min
Total Floating time	>12 (hrs)	>12(hrs)



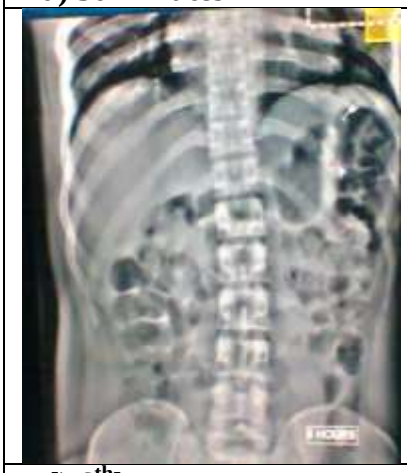
7 a) 30 minutes



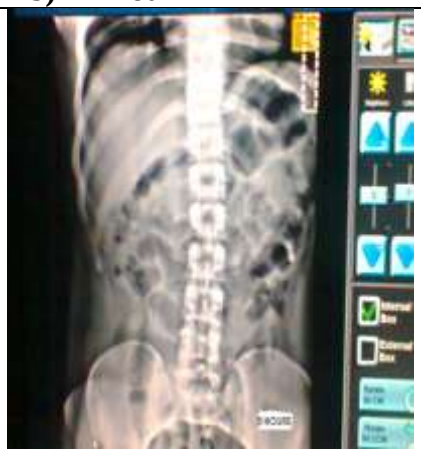
7 b) 2nd hour



7 c) 4thhour



7 d) 6thhour



7 e) 9thhour

Radio graphic images showing the presence of a $Baso_4$ loaded floating tablet in the stomach at different time periods in fed condition (The tablet is indicated with an arrow). The tablets altered its position in the stomach. Images were taken after a) 30 min, b) 2nd hour, c)4th hour, d) 6thhour, e) 9thhour.

Results of *In vivo* X-ray studies

The gastric resident time of optimized Dipyridamole floating matrix tablets were evaluated by conducting *in vivo* X-ray studies in healthy human volunteer. From the radio graphic images following results were obtained.

Condition	Gastric Residence time
Fed state	Up to 6 hours

From the results it was observed that the GRT for the developed Dipyridamole floating effervescent matrix tablets was up to 6 hrs in fed condition. The behavior of the floating tablet in the stomach of human volunteer was observed in real time using a radio graphic images made 30min after the administration, The tablets were observed in human stomach In the next picture taken at 2nd hr significant changes were detected. The tablet had altered its position and turned around. This provided evidence that the tablets did not adhere to the gastric mucosa but on the contrary, floated on the gastric fluid. Additionally the swelling of the tablet was visualized very well together with the white drug core and transulant swelling layer around it. As the swelling layer continued, the glassy core diminished, the swelling later eroded from the outer surface and size reduction was seen and after 9th hour the tablet completely disappeared.

CONCLUSION

Gastro-retentive Floating effervescent matrix tablets of Dipyridamole could be Successfully prepared by using different polymers by HPMC K4M, HPMC K15M, HPMC K100M . It was conclude that the prepared floating effervescent matrix tablets of Dipyridamole containing polymer HPMC K15 formulation (FS5) is the optimized formulation among all formulations. It showed floating lag time 48 sec and floating time > 12hrs. It showed maximum drug release of 99.12% at 12th hour and In vivo X-Ray studies in feed condition showed a gastric residence time for more than 6 hours.

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