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FORMULATION AND EVALUATION OF FLOATING MINI MATRIX TABLETS OF THIAMINE MONONITRATE

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ABSTRACT

Oral route is the most common route of administration of drugs because of the several advantages this offers. The advantages include the ease of administration, least aseptic constraints and the ease of the manufacture of the dosage form. In the present research Floating mini matrix tablets of Thiamine mono nitrate were successfully prepared with hydrophilic polymers like HPMC K_4M, HPMC $K_{15}M$ and HPMC $K_{100}M$ with 5% sodium bicarbonate by wet granulation method with drug**:** polymer ratios of 1:2,1:3,1:4,1:5,1:6. The buoyancy of mini tablets might be due to release and entrapment of carbon dioxide gas in the polymer matrix. Evaluation parameters of powder blend like bulk density, tapped density, Hausner's ratio, Compressibility index, Angle of repose were carried out and results showed that the powder has good flow properties The mechanism of drug release was found to be fickian diffusion except for F1 and F3 which followed erosion and all the formulations followed first-order release kinetics. X-ray radiography studies indicated that the optimized formulations floated in the stomach for sufficient time period without any adhesion to the walls of the stomach. Formulated tablets gave satisfactory results for various evaluation parameters like thickness(4mm), hardness(5-6Kg/cm^2), weight variation(+/- 10%), friability(less than 0.9%), content uniformity(90%-110%), *in vitro* buoyancy properties (around 12hrs)and *in vitro* drug release. **F4,F9,F13** formulations were found to be within desired drug release and floating characteristics and among these formulation **F9** with lesser floating lag time and drug release more than 90 % was considered to be optimized formulation.

INTRODUCTION

Oral route is the most common route of administration of drugs because of the several advantages this offers. The advantages include the ease of administration, least aseptic constraints and the ease of the manufacture of the dosage form. Another great advantage that oral route offers for formulation design is it has variable and versatile physiological conditions at different parts starting from mouth. These enabling developing formulations that can be selectively release the medicament for optimal absorption and therapeutic advantage. Among the oral dosage forms tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer. Tablets account for more than 80% of all pharmaceutical dosage forms administered to people.[1]

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] Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability. But an ideal drug delivery system is one which provides the drug only when and where it is needed, and in the minimum dose level required to elicit the desired therapeutic effects**.** 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.

GASTRORETENTIVE DRUG DELIVERY SYSTEMS[3]

ANATOMICAL AND PHYSIOLOGICAL FEATURES

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, gastroretentive 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.

APPROACHES TO GASTRIC RETENTION[4,5]

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach shown in the following figure.

These systems include

A. Floating systems

B. Bioadhesive systems

C. Swelling and expanding systems

D. High density systems and

E. Modified systems

Mini tablet system

Mini tablets are compressed to 2-3 mm in diameter may be prepared are coated with conventional coating pan to have varying drug release characteristics. Then they may be placed in a gelatin capsule shell to provide a desired pattern of drug release.[6]

This approach consists of 3 steps.

- Wet granulation
- Compression
- Coating

As we all previous know the process of wet granulation which include either aqueous or non aqueous granulation it depends on the characteristic of the drug and further the compression is done by using 3-4 mm punch with the help of the compression machine, further if necessary coating is included the polymers used depends upon the delivery of the drug. The reason for the application of coating on mini tablets to provide chemical stability, improve physical characteristics and enhance patience acceptance. On the whole we can say that the preparation of the mini tablets is comparatively easier[7]

Thiamine is a vitamin, also called vitamin B1. Vitamin B1 is found in many foods including yeast, cereal grains, beans, nuts, and meat. It is often used in combination with other B vitamins, and found in many vitamin B complex products. Vitamin B complexes generally include vitamin B1 (thiamine).[8,9] People take thiamine for conditions related to low levels of thiamine (thiamine deficiency syndromes), including beriberi and inflammation of the nerves

outside the brain (peripheral neuritis) associated with pregnancy or with a vitamin-deficiency disease called pellagra.[10]

MATERIALS AND METHODS

Thaimine mononitarte is Gift sample from AET Labs, Hyderabad ,HPMC K_4M, HPMC $K_{15}M$ and HPMC $K_{100}M$ were gift samples from Dr.Reddy's lab,Hyderabad.Lactose (Anhydrous) Sodium bicarbonate, Talc, PVP K30 and Magnesium stearate Finar reagents, are from local chemical suppliers, Warangal.

FORMULATION DEVELOPMENT

PREPARATION OF MINI MATRIX TABLETS OF THIAMINE MONO NITRATE

Technology Applied : Wet Granulation.

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: Anhydrous lactose
- Antiadherant: Talc
- Lubricant: Magnesium Stearate.

PREPARATION OF MINITABLETS

The mini tablets of this work were prepared by using wet granulation technique. In a mortar the drug along with all the excipients like polymers, lactose, sodium bicarbonate were mixed according to geometric dilution and passed through sieve No.12.Then the nonaqueous granulation is done by using the 10% of PVP solution.The wet mass was passed through sieve No.16.The obtained granules were dried and magnesium stearate , talc were added. Compression was done using 4mm punch. In this work according to the tablet weight ten mini tablets were filled into a single capsule.

TABLET COMPOSITION OF FLOATING MINI MATRIX TABLETS OF THIAMINE MONONITRATE

Table No.1: FORMULATIONS DEVELOPED

SNo.	Thiamine	HPMC K4M	HPMC K15M	HPMC K100M	Lactose	Sodium bicarbonate	Mg.stearate	Talc
1	5	10	-	-	31	2.5	0.5	1
2	5	15	-	-	26	2.5	0.5	1
3	5	20	-	-	21	2.5	0.5	1
4	5	25	-	-	16	2.5	0.5	1
5	5	30	-	-	11	2.5	0.5	1
6	5	-	10	-	31	2.5	0.5	1
7	5	-	15	-	26	2.5	0.5	1
8	5	-	20	-	21	2.5	0.5	1
9	5	-	25	-	16	2.5	0.5	1
10	5	-	30	-	11	2.5	0.5	1
11	5	-	-	10	31	2.5	0.5	1
12	5	-	-	15	26	2.5	0.5	1
13	5	-	-	20	21	2.5	0.5	1
14	5	-	-	25	16	2.5	0.5	1
15	5	-	-	30	11	2.5	0.5	1

Each mini tablet weight is 50mg, 10 mini tablets are filled in one gelatin capsule.

In -Vitro Drug Release Characteristics:

The *in vitro* drug release study was performed for the single- & multiple-unit tablets using USP Type II dissolution apparatus under the following conditions.

Dissolution test parameters

Medium	**:**	900ml of 01.N HCl
Rotation speed	**:**	50 rpm
Temperature	**:**	37±0.1ºC
Sampling Volume	**:**	5ml
Sampling Time	**:**	0.5, 1, 1. 5, 2, 3, 4,5, 6, 8, 10, 12 hours

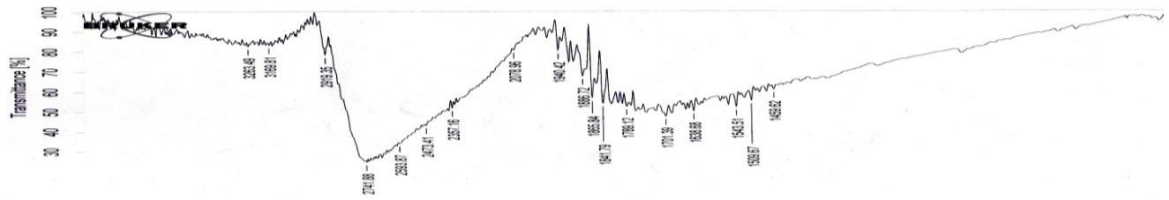
At predetermined time intervals samples (5 ml) were collected and replenished with same volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer at 246 nm.

RESULTS AND DISCUSSION

DRUG-EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared Spectroscopy (FT-IR)

The thermal behavior of pure drug and the respective excipients and the binary mixture of



drug and excipients are compared in the FT-IR thermogram

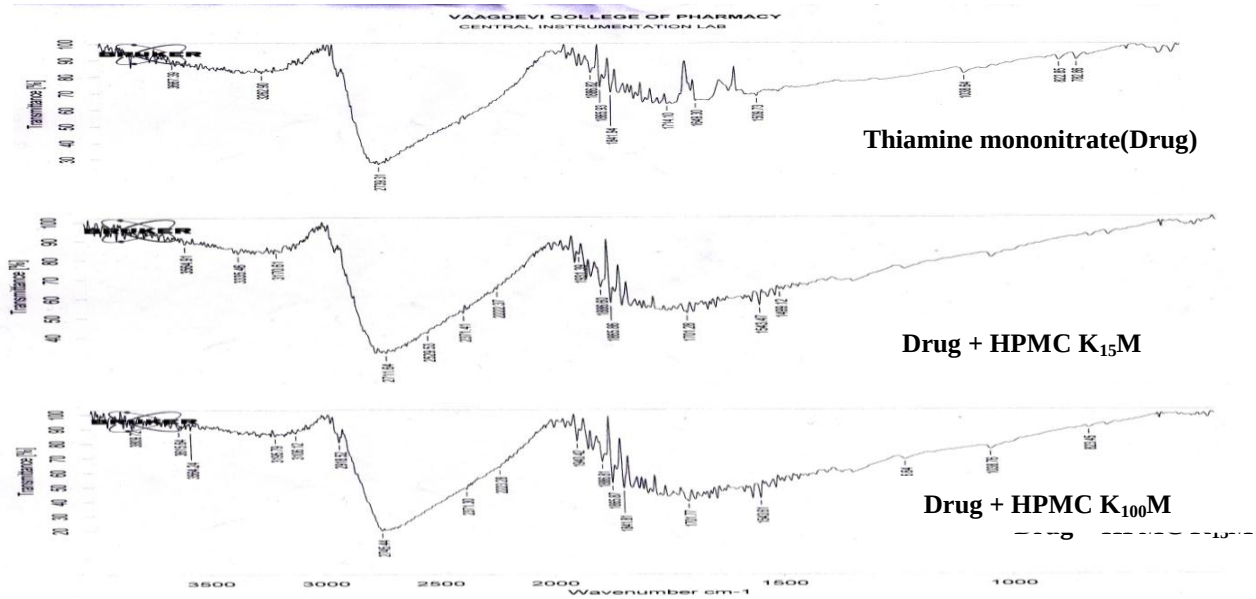


Figure No.1: FTIR SPETRUM

Table No.2: FTIR Results

Functional group	Absorption range	Pure drug	Drug+HPMC K $_4$M	Drug+HPMC K $_{15}$M	Drug+HPMC K $_{100}$M
Alcohol/phenol O-H(stretch)	3550 3200	3667.39	3564.91	3283.4	3584.24
Amine N-H(stretch)	3500-3300	3262.90	3335.48	3169.81	3195.79
C-O(bending)	1300-1000	1038.64	1098.71	1340.42	1038.78
-C=C-(stretch)	2260-2100	2139.31	2222.37	2078.96	2223.38
-C-H-(scissoring,bending)	1470-1380	1409.73	1499.12	1459.62	1226.64

FT-IR was employed to ascertain the compatibility of thiamine with polymers.The individual drug and drug with polymers were separately scanned and the spectras were compared for conformation of common peaks. Thiamine with polymers showed no significant variation in height, intensity and position of peaks, suggesting that drug and excepients were compatible.

There is no interaction between drug and polymer. Hence it can be concluded that the drug is in free state and can release easily from the formulation.

PHYSICAL PROPERTIES OF PREPARED POWDER BLENDS

Physical properties like Compressibility index (CI), Angle of repose and Hausner ratio were calculated and tabulated.The results were in the limits and comply with the standard.

Table No.3: Precompression Results of powder blend.

Formulation	CI	Angle of Repose	Hausner ratio	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)
F1	12.3	26.8^o	1.14	0.396	0.465
F2	15.9	27.5^o	1.18	0.394	0.456
F3	12.8	28.0^o	1.13	0.382	0.449
F4	15.7	29.4^o	1.18	0.391	0.459
F5	12.4	28.5^o	1.14	0.387	0.441
F6	11.2	29.4^o	1.13	0.395	0.468
F7	13.6	28.4^o	1.02	0.399	0.474
F8	12.5	26.9^o	1.16	0.393	0.460
F9	14.6	27.5^o	1.15	0.388	0.456
F10	12.9	28.5	1.12	0.396	0.459
F11	12.4	28.7	1.11	0.392	0.465
F12	14.1	29.1	1.05	0.387	0.442
F13	15.5	27.5	1.14	0.394	0.469
F14	14.7	28.8	1.18	0.392	0.450
F15	11.8	27.6	1.09	0.393	0.463

EVALUATION OF PHYSICAL PARAMETERS OF FLOATING MINITABLETS OF THIAMINE MONONITRATE.

All the prepared formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeial limits. 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.

Table No.4: Results of Hardness, Thickness, Weight variation, Friability:

Formulations	Hardness(kg/cm^2) (kg/cm^2)± S.D n=6	Thickness(mm) (mm) ± S.D n=10	Weight Variation(mg) (mg)± S.D n=20	Friability (%) n=20	Drug content (%)±SD n=3
F1	5.15 ± 0.01	2.99 ± 0.04	50 ± 1.12	0.14	99.23± 1.2
F2	5.11 ± 0.05	2.99 ± 0.03	49 ± 1.15	0.15	100.12± 1.5
F3	5.20 ± 0.02	2.98 ± 0.06	49± 1.12	0.18	99.82± 2.0
F4	5.15 ± 0.02	2.99 ± 0.05	50 ± 1.10	0.15	99.98± 1.0
F5	5.18 ± 0.01	2.98 ± 0.02	50.5±1.15	0.17	99.43± 2.1
F6	5.15 ± 0.03	2.97 ± 0.03	50.1±1.12	0.15	99.67± 1.4
F7	5.17 ± 0.05	2.99 ± 0.04	50 ± 1.01	0.16	98.89± 1.1
F8	5.23 ± 0.05	2.98 ± 0.07	49 ± 1.14	0.18	100.23± 1.2
F9	5.11 ± 0.05	2.99 ± 0.05	50 ± 1.13	0.19	99.95± 2.1
F10	5.06 ± 0.09	2.99 ± 0.02	50.2±1.10	0.16	101.10± 1.1
F11	5.18 ± 0.08	2.98 ± 0.04	48 ± 1.11	0.18	98.88± 2.2
F12	5.14 ± 0.01	2.98 ± 0.03	49 ± 1.10	0.17	100.14± 1.0
F13	5.08 ± 0.07	2.99 ± 0.06	51 ± 1.0	0.14	100.01± 1.1
F14	5.21 ± 0.02	2.98 ± 0.02	49 ± 1.15	0.13	98.99± 2.1
F15	5.16 ± 0.06	2.99 ± 0.04	50 ± 1.14	0.14	101.21±1.0

SD=standard deviation.

The results of the physical tests of the formulations were in the limits and comply with the standards. Hence it was considered that they have good physical properties and can withstand the mechanical shocks.

FLOATING PROPERTIES OF FLOATING MINI MATRIX TABLETS OF THIAMINE MONONITRATE

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.

Table No.5: Floating Properties of Mini Tablets

Formulation code	Floating Lag time±SD (sec),n=10	Total floating time±SD (hrs), n=10
F1	75±0.21	4.3±0.01
F2	69±0.15	6.4±0.02
F3	57±0.12	8±0.01
F4	39±0.11	>12±0.01
F5	46±0.13	>12±0.03
F6	71±0.11	7.6±0.01
F7	68±0.12	8.8±0.02
F8	55±0.13	10±0.03
F9	35±0.11	>12±0.01

F10	44±0.21	>12±0.02
F11	67±0.15	9.1±0.01
F12	53±0.13	11.2±0.03
F13	36±0.11	>12±0.01
F14	42±0.12	>12±0.02
F15	68±0.14	>12±0.02

Table No.6: Percentage drug release of mini matrix tablets of thiamine mononitrate with HPMC K_4M

Time(h)	Percentage drug release				
	F1,n=3 mean±SD	F2 ,n=3 mean±SD	F3 ,n=3 mean±SD	F4 ,n=3 mean±SD	F5 ,n=3 mean±SD
0	0	0	0	0	0
0.5	27.22± 1.9	25.437±1.63	22.17±2.15	18.85±2.78	12.27±2.51
1	50.21±1.12	49.202±2.02	45.45±1.72	39.46±1.98	23.89±2.48
1.5	59.34±0.57	58.403±1.22	52.78±1.98	45.21±1.34	37.99±1.99
2	73.67±1.42	71.499±1.71	59.01±1.23	50.11±1.65	43.87±1.22
3	81.89±1.23	80.301±1.34	62.86±1.45	56.23±1.78	49.99±1.93
4	85.83±1.20	84.995±1.13	74.69±1.89	66.46±1.67	56.46±2.61
6	93.99±1.51	92.623±1.46	80.15±1.21	77.77±2.01	62.09±2.98
8	96.45±0.61	95.589±0.75	92.91±0.88	90.45±1.46	69.67±2.67
10	98.43±0.37	97.257±0.42	97.54±0.35	95.98±1.11	78.88±1.91
12	99.91±0.02	99.857±0.01	99.89±0.02	98.01±0.21	85.46±1.72

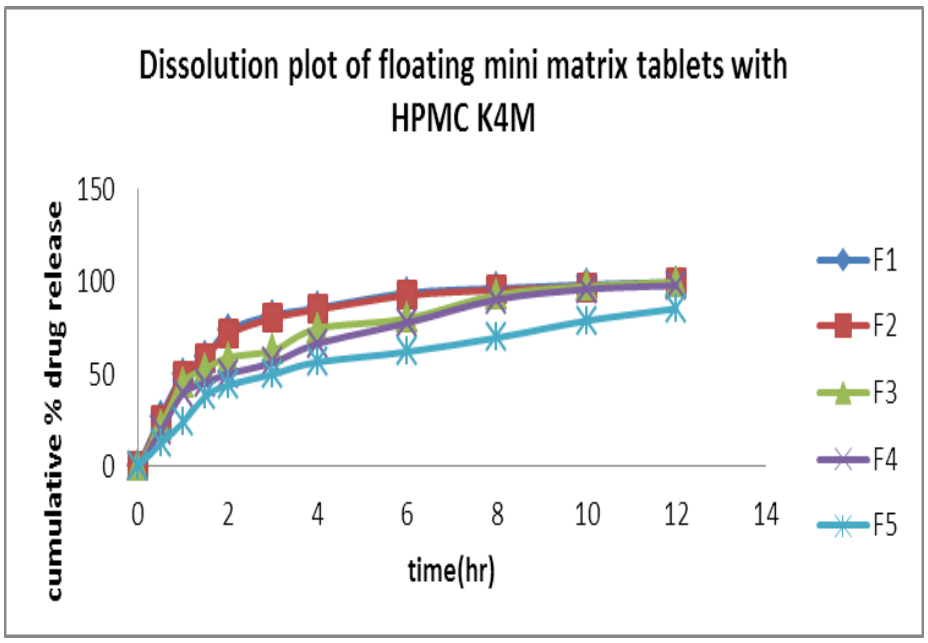


Figure No.2: Dissolution plot of floating mini matrix tablets with HPMC K_4M

Table No.7: Percentage drug release of mini matrix tablets of thiamine mononitrate with HPMC K15M

Time(h)	Percentage drug release				
	F6,n=3 mean±SD	F7,n=3 mean±SD	F8,n=3 mean±SD	F9,n=3 mean±SD	F10,n=3 mean±SD
0	0	0	0	0	0
0.5	22.11±2.21	20.09±2.91	18.9±2.94	18.85±2.89	11.09±2.82
1	43.87±2.01	40.87±2.78	39.23±2.55	39.12±2.59	28.78±2.78
1.5	52.09±1.98	49.74±2.94	48.89±2.47	45.21±2.41	37.56±2.91
2	69.89±2.67	64.12±2.46	55.78±2.11	50.11±2.12	43.33±2.99
3	78.67±2.46	75.34±2.99	62.12±2.19	56.23±1.98	56.23±2.71
4	85.83±1.21	82.22±1.51	69.45±2.01	66.46±1.97	62.89±1.67
6	91.07±1.05	90.67±1.01	75.34±1.91	75.09±1.43	71.11±1.47
8	94.89±0.96	92.36±1.13	80.04±1.22	80.01±1.89	80±1.56
10	96.78±0.15	95.89±1.11	91.45±1.12	93.13±1.01	86.46±1.11
12	99.12±0.05	98.87±0.01	96.34±0.19	96.33±0.91	89.88±1.97

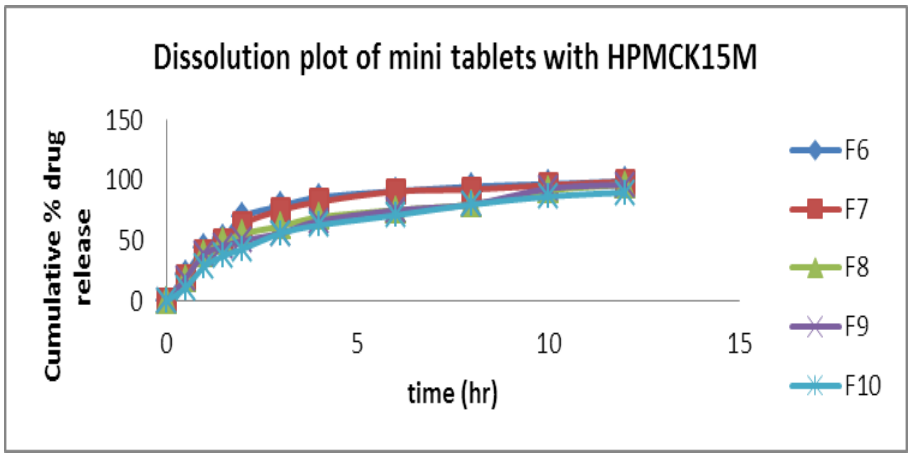


Figure No.3: Dissolution plot of floating mini matrix tablets with $K_{15}M$

Table No.8: Percentage drug release of floating mini matrix tablets of thiamine mononitrate with HPMC K100M

Time(h)	Percentage drug release				
	F11,n=3 mean±SD	F12,n=3 mean±SD	F13,n=3 mean±SD	F14,n=3 mean±SD	F15,n=3 mean±SD
0	0	0	0	0	0
0.5	21.46±2.62	19.67±2.51	11.13±2.99	9.59±2.99	6.95±2.94
1	40.89±2.15	33.56±2.26	24.67±2.56	13.7±2.22	11.06±2.89
1.5	50.09±2.54	43.65±2.67	37.78±2.45	21.62±2.45	19.27±2.78
2	69.98±1.99	59.89±2.88	48.98±2.58	37.75±2.58	37.17±2.66
3	78.67±1.78	71.67±2.14	60.07±2.51	45.38±2.81	44.21±2.53
4	85.38±1.57	80.32±2.23	69.12±1.96	54.77±2.93	51.54±2.39
6	91.01±1.24	90.99±1.58	77.32±1.99	67.09±2.89	68.85±2.43
8	94.22±1.11	94.02±1.78	86.88±2.01	77.89±2.16	78.54±2.16
10	97.56±1.05	96.98±1.01	91.09±1.78	82.64±2.71	80.13±1.97
12	99.01±0.12	98.88±0.56	94.65±1.05	88.22±1.78	82.64±1.13

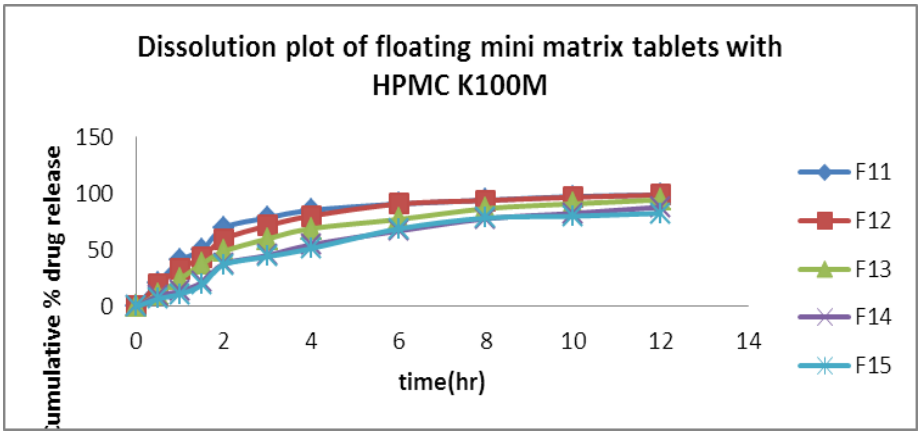


Figure No.4: dissolution plot of floating mini matrix tablets with HPMC K100M

Table No.9: In Vitro dissolution kinetics of floating mini matrix tablets of thiamine mononitrare

Formulation No.	Correlation coefficient (r2)				Diffusional exponent,n
	Zero order	First order	Korsemeyer peppas	Higuchi plot	
F4	0.847	0.982	0.949	0.978	0.309
F9	0.835	0.9634	0.941	0.9728	0.246
F13	0.826	0.9931	0.915	0.952	0.238

SWELLING STUDIES

Determination of swelling index of tablets

Radial swelling of the matrices was monitored by immersing the tablet in beaker containing dissolution medium (250ml, 37^0 C). At predefined time interval, an increase in the tablet diameter was determined over a specified period of time. The same measured in atleast two different axes perpendicular to each other and their mean value is taken.

Method

The temperature of beaker containing 250ml double distilled water (dissolution medium) was maintained at 37.5 ± 0.5 ^{0} C. The scale was placed below the beaker so that scale could be easily shown. The diameter of the tablet was initially measured and then it was put inside the beaker. The tablet was placed such that diameter could be measured at specific time interval without taking the tablet out of the medium.

Table No.10: Swelling Index of HPMC K_4M, HPMC $K_{15}M$ and HPMC K100M Polymer tablets.

Time (hrs)	HPMC K4M	HPMC K15M	HPMC K100M
0.5	25	17	12.5
1	43.75	34.5	25
2	62.5	48	37.5
3	87.5	62.25	50
4	100	76.5	62.5
6	106.25	84	75
8	112.5	93.75	81.25
10	117.5	99.5	87.5
12	117.5	104.25	93.75
24	-	106	99.25

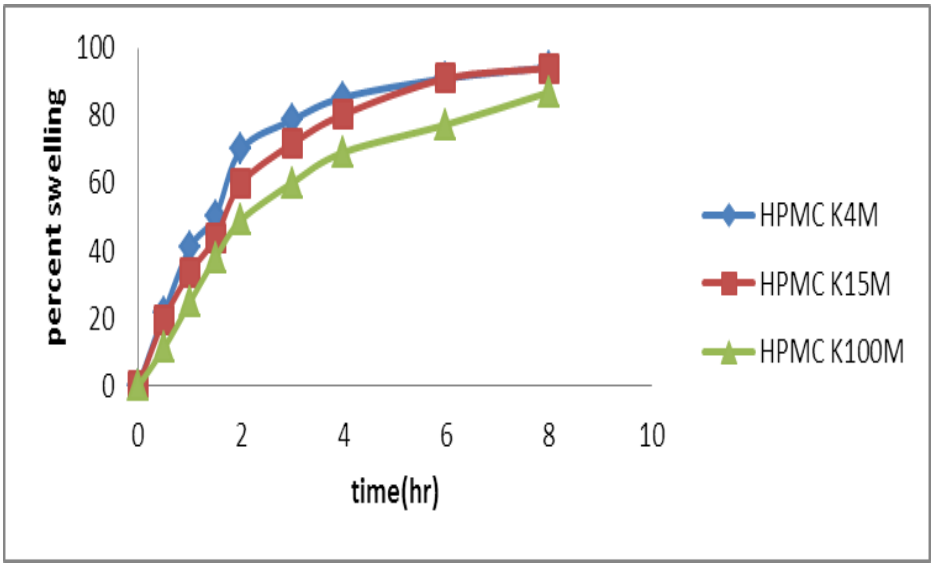


Figure No.5: Percent swelling Vs time for HPMC K4M, HPMC K15M and HPMC K100M polymer

STABILITY STUDIES

The best formulation of Thiamine mononitrate floating mini matrix tablets containing HPMC and HPMC K100M were subjected to stability study by keeping them at 40 °C/75% RH for 1 month to assess their stability with respect to their physical appearance, drug content, floating properties and release characteristics. The physical characteristic like weight variation, hardness, friability, percent drug content and in vitro release profile were determined at interval of 2 weeks and 4 weeks.

Table No.11: Physicochemical Characteristics of Thiamine floating mini matrix tablets during stability study period (40 °C/75% RH)

Formulation	Stability study period	Weight Variation (mg) S.D (n=10)	Hardness (kg/cm^2) S.D (n=10)	Friability (%) (n=20)	Drug content (%) S.D (n=3)
F4	0 day	501.1	5.150.02	0.150.01	99.980.56
	2^{nd} week	502.1	5.50.15	0.250.15	100.260.64
	4^{th} week	491.17	5.00.35	0.320.35	101.570.47
F9	0 day	501.13	5.110.05	0.190.02	99.950.39
	2^{nd} week	491.86	5.40.53	0.220.53	101.530.76
	4^{th} week	501.12	5.20.67	0.520.67	100.20.51
F13	0 day	511.0	5.080.07	0.140.04	100.10.39
	2^{nd} week	501.1	5.40.53	0.450.53	101.50.76
	4^{th}week	491.3	5.20.67	0.250.67	99.70.51

Table No. 12: Floating parameters during stability study period (40 °C/75% RH)

Formulation	Stability study period	Floating lag time (min)	Floating time (hrs)
F4	0day	0.39	12
	2^{nd} week	0.41	12
	4^{th} week	0.38	12
F9	0 day	0.35	12
	2^{nd} week	0.42	12
	4^{th} week	0.32	12
F13	0 day	0.36	12
	2^{nd} week	0.38	12
	4^{th}week	0.41	12

Table No:13 Dissolution profile of F9 at 0, 2^{nd} week and 4^{th} week during the stability period

Time (hrs)	Cumulative % drug release		
	0 day	2nd week	4th week
0	0	0	0
0.5	9.59	11.23	8.12
1	13.7	14.12	12.08
1.5	21.62	24.01	18.88
2	37.75	41.67	33.26
3	45.38	48.43	42.65
4	54.77	56.98	52.45
6	67.09	69.99	66.12
8	77.89	79.34	76.01
10	82.64	83.15	80.89
12	88.22	89.67	86.48

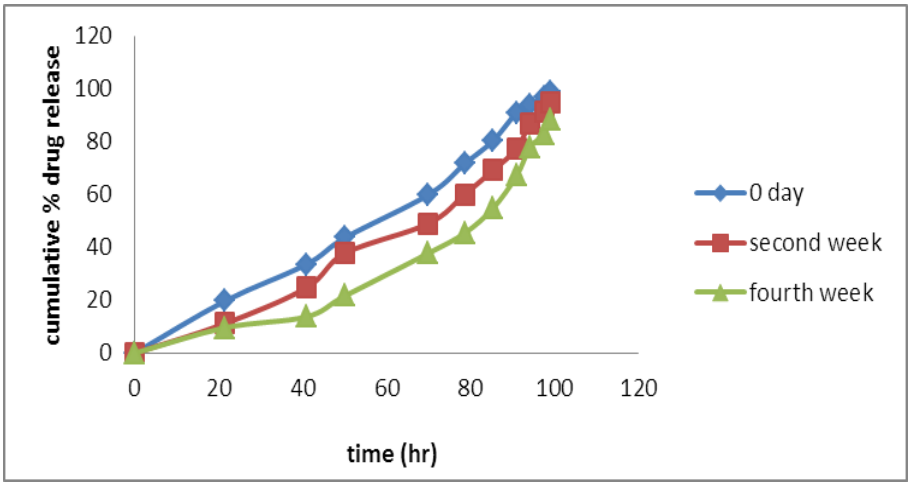


Figure No.6: Dissolution plot of F9 at 0, 2nd week and 4th week during the stability period.

Table No.14: Dissolution profile of F9 at 0,2nd and 4th week during the stability period

Time (hrs)	Cumulative % drug release		
	0 day	2nd week	4th week
0	0	0	0
0.5	11.13	9.56	13.01
1	24.67	20.12	26.19
1.5	37.78	33.78	40.32
2	48.98	45.01	52.11
3	60.07	58.43	63.83
4	69.12	64.11	70.84
6	77.32	75.23	79.93
8	86.88	84.29	87.42
10	91.09	89.03	91.99
12	94.65	93.28	95.21

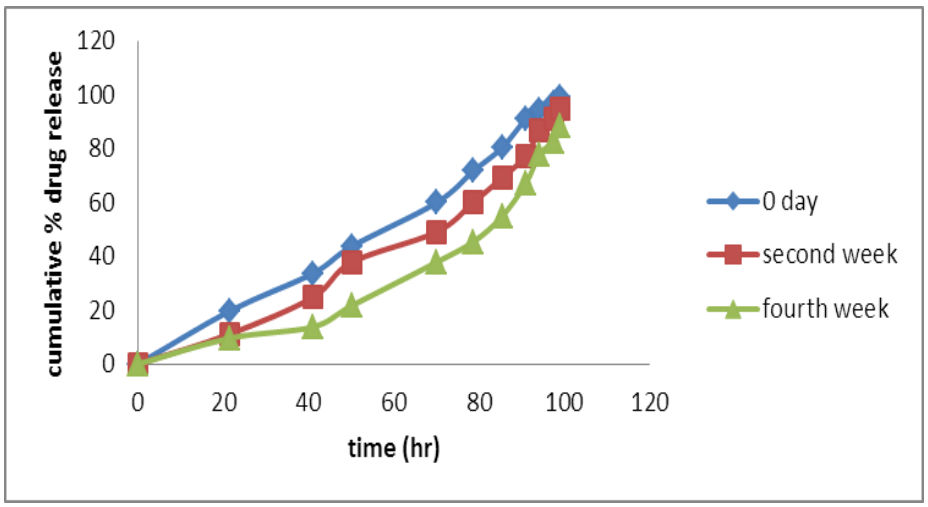


Figure No.7: Dissolution plot of F9 at 0, 2nd week and 4th week during the stability period

X-RAY STUDIES OF FORMULATION F9

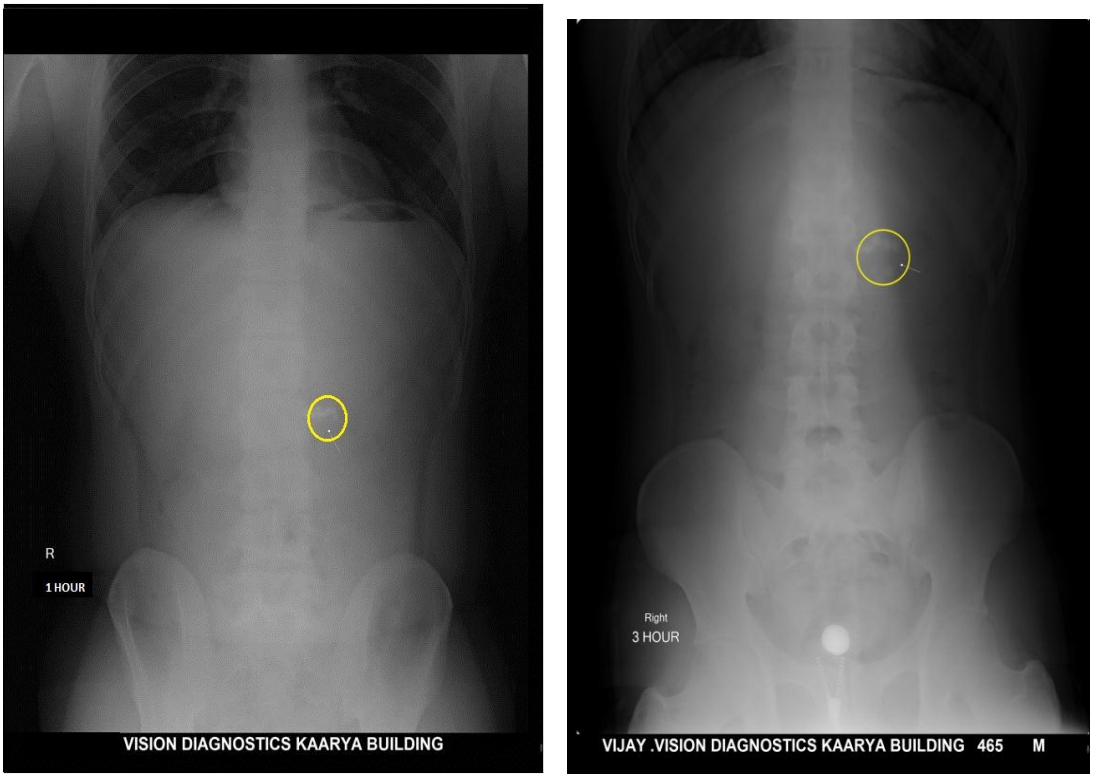


FIGURE .NO 8A, 8B -X-RAY

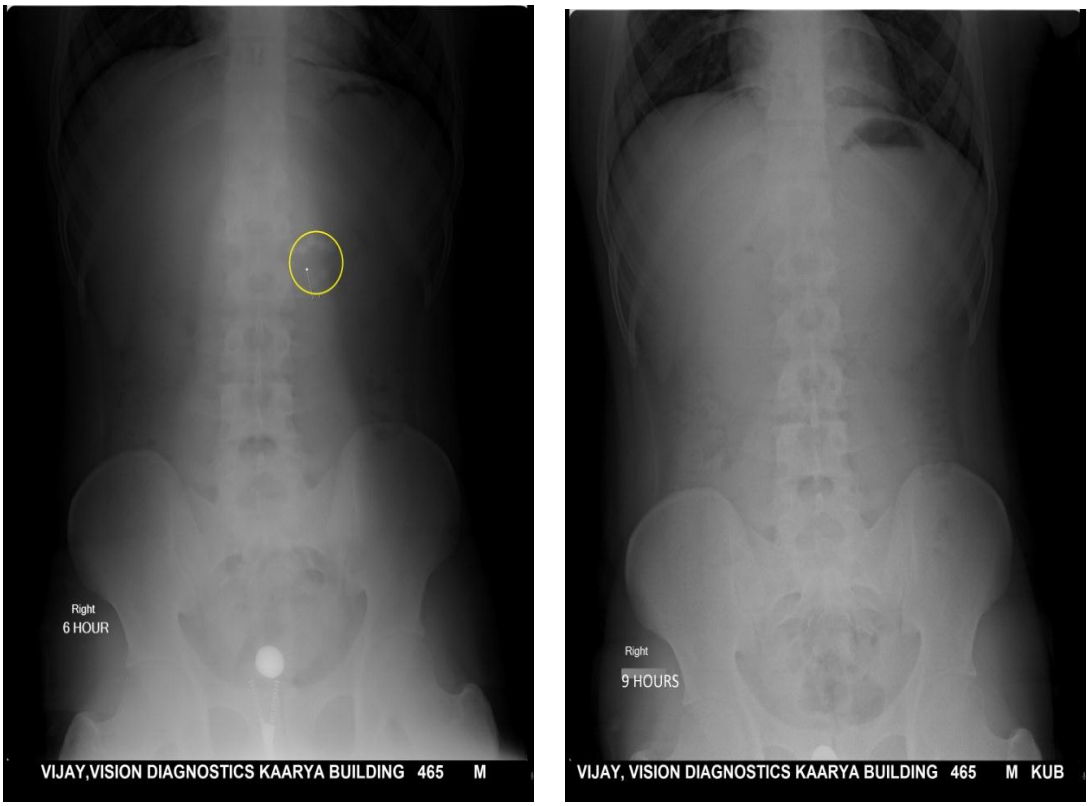


FIGURE .NO 8C, 8D- X-RAY

The in-vivo X-ray studies were approved by the institutional ethical committee with approval No.IHEC/VGOPC/028/2013.Tablets were administered to 2 healthy human volunteers aged 20-25 years and weighing 50-60kgs were selected for these studies. For these studies, optimized floating formulation F4 was modified by replacing 3 mg of Thiamine mononitrate 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 with 200ml of water and for next 4hrs at 30min interval 200ml of water was given.The mini tablets floated efficiently for 6hrs in the stomach without any adhesion to the walls of the stomach.

DISCUSSION

- Floating mini matrix tablets of Thiamine mono nitrate were successfully prepared with hydrophilic polymers like HPMC K_4M, HPMC $K_{15}M$ and HPMC $K_{100}M$ with 5% sodium bicarbonate by wet granulation method with drug **:** polymer ratios of 1:2,1:3,1:4,1:5,1:6. The buoyancy of mini tablets might be due to release and entrapment of carbon dioxide gas in the polymer matrix.
- Evaluation parameters of powder blend like bulk density, tapped density, Hausner's ratio, Compressibility index, Angle of repose were carried out and results showed that the powder has good flow properties.
- FT-IR studies showed no incompatibility between drug, polymer and various excipients used in the formulations. The optimized formulations were subjected to FTIR studies to confirm that there are no drug polymer interactions. The result indicated the absence of interaction because the major functional groups which were present in the pure drug were also present in the mixtures of drug and polymer without any much variations in the peak values. It presumably suggests that the drug molecule is present in an unchanged state in the formulation.
- Formulated tablets gave satisfactory results for various evaluation parameters like thickness(4mm), hardness(5-6Kg/cm^2), weight variation(+/- 10%), friability(less than 0.9%), content uniformity(90%-110%), *in vitro* buoyancy properties (around 12hrs)and *in vitro* drug release.
- Since in the preparation of floating tablets, the floating parameters are most important. Hence formulations which show minimum floating lag time with maximum total floating time were selected. The floating lag time was found to be less for the formulations F4, F9,

F13 with 39sec,35sec,36sec respectively. Even the total floating time was found to be more than 12hrs for **F4, F9, F13** formulations with more than 90%drug release upto 12hrs.

- The thiamine floating mini matrix tablets were subjected to in vitro drug release studies in 0.1N HCl (pH1.2) for 12 hours to access the ability of the formulation for providing controlled drug delivery using USP Type2 (paddle) apparatus , maintained at 37 ± 0.5^0C with 50rpm.
- Formulations with HPMC K4M, F1 to F3 released more than 90% of drug within 6 hrs whereas formulation F4 and F5 released 98.01% and 85.46% respectively in 12 hours. As F4 released more drug than F5, hence **F4** is considered as an optimized formulation in the case of HPMC K4M.
- Formulations with HPMC K15M, F6 and F7 released more than 90% of drug within 6 hrs whereas formulation F8,F9 and F10 released 96.32%,96.33% and 89.88% respectively in 12 hours. As F9 released more drug than F8 and F10 and FLT of F9 is less when compared to others **F9** is considered as an optimized formulation in the case of HPMC K15M.
- Formulations with HPMC K100M, F11and F12 released more than 90% of drug within 6 hrs whereas formulation F13, F14 and F5 released 94.65%, 88.22% and 82.64% respectively in 12 hours. As **F13** released more drug than F14 and F15 it is considered as an optimized formulation in the case of HPMC K100M.
- The correlation of coefficient (r^2) of the HPMC K4M , HPMC K15M and HPMC K100M floating mini matrix tablets for first order release kinetics was found to be higher when compared to that of zero order release kinetics indicating that drug release followed first order kinetics.
- The dissolution data were further characterized by fitting the data into Higuchi's square root time model. The correlation coefficient values of Higuchi plot of formulations F1 to F15 were found to be in the range of 0.8607 to 0.9736. As the correlation coefficient values are close to one, it indicates that the drug release is by diffusion mechanism.

  When the log cumulative percent of drug released was plotted against time on log scale, the diffusional exponent values (n) were found to be less than 0.45 for all the formulations except F1 and F3 indicating that the release from F1 and F3 followed non-fickian diffusion i.e.,erosion and remaining all the formulations followed fickian diffusion.From the above observations it was *in vitro* drug release. **F4,F9,F13** formulations were found to be within desired drug release and floating characteristics

and among these formulation **F9** with lesser floating lag time and drug release more than 90 % was considered to be optimized formulation.

- The swelling studies were carried for 24 hrs. The results indicate that the selected polymers were of swellable type and HPMC K4M have marginally more swellability than HPMC K15M and HPMC K100M matrices.
- X-ray studies were conducted invivo by replacing 3gm of drug with barium sulphate in F4 formulation and found that the mini tablets floated efficiently for 6hrs in the stomach without any adhesion to the walls of the stomach.

CONCLUSION

The following conclusions can be drawn from the results obtained.

- Preformulation studies of the drug were reported within the Pharmacopeial limits and the drug excipient compatibility FT-IR studies indicated no interactions. Floating lag time and total floating period for the optimized formulations were found to be acceptable. The hardness, thickness, friability, weight variation, drug content, swelling index and in-vitro release were uniform and reproducible and reported within the Pharmacopeial limits.
- The mechanism of drug release was found to be fickian diffusion except for F1 and F3 which followed erosion and all the formulations followed first-order release kinetics.
- X-ray radiography studies indicated that the optimized formulations floated in the stomach for sufficient time period without any adhesion to the walls of the stomach.

Hence it is concluded that the adopted method successfully yielded uniform and reproducible floating mini matrix tablets of thiamine mononitrate with HPMC K_4M,$K_{15}M$,$K_{100}M$ polymers which was confirmed by in-vitro and in-vivo studies**.,** Thiamine mononitrate.

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