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FORMULATION AND CHARACTERIZATION OF FLOATING DOXOFYLLINE TABLETS

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ABSTRACT

In the present work, an attempt has been made to develop gastro retentive floating tablets of Doxofylline, HPMC K4M and carbopol were used as controlled release polymers**.** All the formulations were prepared by direct compression method on 12 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. FH 5 was the best optimized floating formulation because it released drug completely in 12hrs.It was also observed that the increasing concentration of polymers had a retarding effect on the drug release from the polymer matrices.

INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached [1].

Although some important applications, including oral administration of peptide and protein drugs, can be used to prepare colonic drug delivery systems, targeting drugs to the colon by the oral route. More often, drug absorption is unsatisfactory and highly variable among and between individuals, despite excellent in vitro release patterns. The reasons for this are essentially physiological and usually affected by the GI transit of the form, especially its gastric residence time (GRT), which appears to be one of the major causes of the overall transit time variability [2].

Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy [3,4,5].Doxofylline is a member of methyl xanthines structurally related to theophylline, used in clinical management of patients with obstructive respiratory disorders, in particular Chronic Obstructive Pulmonary Disorder (COPD) and Asthma. The elimination half life of Doxofylline is 7 hrs which indicated its suitability in formulating into a sustained release dosage form. The oral bioavailability of Doxofylline has been reported to be 60%.Due to its high solubility in acidic medium (pH 1.2), prolonged gastric retention of doxofylline may offer numerous advantages, including, increase in the extent of absorption, improved bio-availability and therapeutic efficacy. Frequent administration of Doxofylline (400mg b.i.d/t.i.d) also prompted to make floating sustained release tablets of Doxofylline. Based on this, an attempt was made through this investigation to formulate floating matrix tablets of doxofylline using different polymers. The solubility and stability of doxofylline in hydrochloric acid helps for better absorption in acidic environment. By employing gastro-retentive floating drug delivery systems, the dosage form is retained in the stomach and the drug is released in a controlled fashion.

METHODOLOGY

Doxofylline obtained as a gift sample from Hetero labs Hyderabad. HPMC K4M, CARBOPOL 970 were obtained from Signet Chemical Corporation, Mumbai, Avicel pH

101, Lactose Mono hydrate, Conc. Hydrochloric acid, Conc. Hydrochloric acid, Aerosil, Sodium bicarbonate obtained from S.D. Fine Chemicals, Mumbai.

PREPARATION OF DOXOFYLLINE FLOATING TABLETS

The Compositions of different formulation trials with different polymers are presented in the Tables 1, 2 and 3. Accurately weighed quantities of polymer, avicel were taken in a mortar and mixed geometrically. To this mixture required quantity of doxofylline was added and mixed slightly with pestle. This mixture was passed through 40# and later collected in a plastic bag and blended for 5 min. To this required amount of sodium bi carbonate was added and again mixed for 5 min. Later required quantity of magnesium stearate and aerosol were added and the final blend was again passed through 40#. Thus obtained blend was mixed thoroughly for 10 min and compressed into tablets with 13mm x 5mm Caplet Punches and corresponding dies at a hardness of 6kg/cm^2 on a rotary tablet punching machine

TABLE 1: FORMULAE USED TO PREPARE DOXOFYLLINE FLOATING TABLETS WITH HPMC K4M.

Ingredients	Composition of Doxofylline Floating Tablets (mg)					
	FH 1	FH 2	FH 3	FH 4	FH 5	FH 6
Doxofylline	600	600	600	600	600	600
Hpmc K4M	60	120	180	240	300	360
Avicel	313.5	253.5	193.5	133.5	73.5	13.5
NaHCO3	110	110	110	110	110	110
Mg.Stearate	5.5	5.5	5.5	5.5	5.5	5.5
Aerosil	11	11	11	11	11	11
TOTAL WEIGHT	1100	1100	1100	1100	1100	1100

Ingredients	Composition of Doxofylline Floating Tablets (mg)				
	FH 7	FH 8	FH 9	FH 10	FH 11
Doxofylline	600	600	600	600	600
Carbopol 970	60	90	120	150	180
Lactose	242	212	182	152	122
NaHCO3	102.5	102.5	102.5	102.5	102.5
Mg.Stearate	10.25	10.25	10.25	10.25	10.25
Aerosil	10.25	10.25	10.25	10.25	10.25
TOTAL WEIGHT	1025	1025	1025	1025	1025

TABLE 2: FORMULAE USED TO PREPARE DOXOFYLLINE FLOATING TABLETS WITH CARBOPOL 970

STANDARD GRAPH OF DOXOFYLLINE

An accurately weighed amount of 100mg doxofylline was transferred into a 100 ml volumetric flask containing 0.1N HCl to dissolve and then the volume was made up to the mark with 0.1N HCl. From this necessary dilutions were made to give concentration ranging from 1-32 µg/ml solutions. The absorbance of the volumetric solutions was recorded at λ_{max} (272nm) of the drug and plotted graphically to give the standard graph of doxofylline.

Evaluation of Precompression Blend

The powder blend of all formulations was evaluated for Bulk density, Tapped density, Compressibility Index, Hausner ratio and Angle of repose.

A) Bulk Density

30gms of material was passed through a sieve no. 25 to break up agglomerates and introduced into a dry 100mL cylinder, without compacting, the powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read. The bulk density was calculated, in grams per ml, using the formula.

$$\mathbf{(M) / (Vo)}$$

Where M = Total weight of the powder blend and V_0 is the bulk volume of the powder blend

B) Tapped Density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a mechanical tapped density tester (Electrolab) that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement was less than 2% and then tapped volume V_f, was measured to the nearest graduated unit. The tapped density was calculated, in g per ml, using the formula:

$$\mathbf{(M) / (V_f)}$$

Where M = Total weight of the powder blend and V_f is the tapped volume of the powder blend

C) Measures of Powder Compressibility

The Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions and a greater difference between the bulk and

tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio, which are calculated using the following formulae [7].

Compressibility Index = **(Vr-Vo) * 100 / Vr**

Where , Vr = Tapped density ; Vo = Bulk density

D) Hausner Ratio:

It is the ratio of bulk density to tapped density

Vo/ Vf

Vo = Bulk density; Vr= Tapped density

E) Angle of Repose

The fixed funnel method was employed to measure the repose angle. A funnel was secured with its tip at a given height, H above a graph paper that was placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius, R, of the base of the conical pile was measured. The angle of repose, α, was calculated using the following formula.

$$\alpha = \tan^{-1} H/R$$

DETERMINATION OF PHYSICAL PARAMETERS OF FLOATING TABLETS [8, 9].

Weight Variation test

Twenty (20) tablets from each batch were individually weighed in grams on an analytical balance. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight

Thickness test

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Vernier Caliperse. The average thickness and standard deviation were reported.

Hardness test

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness, and the standard deviation was reported.

Friability test

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friablator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as per weight loss from the original tablets.

Determination of Drug Content

Ten tablets with pre determined weight from each batch were taken and crushed in a mortar and weight equivalent to one average tablet was taken, transferred to a 250 ml volumetric flask and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and the filtrate was sufficiently diluted and the absorbance was recorded against the blank at 272 nm. The drug content of the Standard containing the drug powder was also determined. The Drug content was determined by the formula[10].

$$\text{Drug content} = \frac{\text{Amount in test}}{\text{Amount in standard}} \times 100$$

The tablet passes the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the stated amount.

***In-vitro* buoyancy Studies.**

The in-vitro buoyancy (n= 3) was determined by floating lag times according to the method described by Rosa et al.The tablets were placed in a beaker containing 100 ml of 0.1N HCL. The time required for the tablet to rise to the surface and float was taken as floating lag time. Total floating time was also measured.

***In vitro* Drug Release Studies**

The release rate of Doxofylline floating tablets was determined using USP Type 2 Apparatus. The dissolution test was performed in triplicate, using 900ml of 0.1N HCL,at 37± 0.5˚C at 50 rpm for 12 hrs. A 5ml sample was withdrawn from the dissolution apparatus at specified time points and the samples were replaced with fresh dissolution medium.The samples were filtered through a 0.45-µm membrane filter and diluted if necessary. Absorbance of these solutions was measured at 272nm using Elico SL -159, U.V-Visible Spectrophotometer. Cumulative drug release was calculated using the equation (y = 0.03x + 0.024) generated from Beer Lambert's Calibration curve in the linearity range of 1-32µg/ml.

Kinetic Analysis of Dissolution Data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent [11]. Higuchi [12] described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian

diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$C = K_0 t$ (1)

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$LogC = LogC_0 - K_1 t / 2.303$ (2)

Where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \quad (3)$$

Where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \quad (4)$$

Where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

STANDARD GRAPH OF DOXOFYLLINE

The standard graph of Doxofylline in 0.1N HCl showed a good linearity with R^2 of 0.999, in the concentration range of 0-32 µg/ml at 272nm

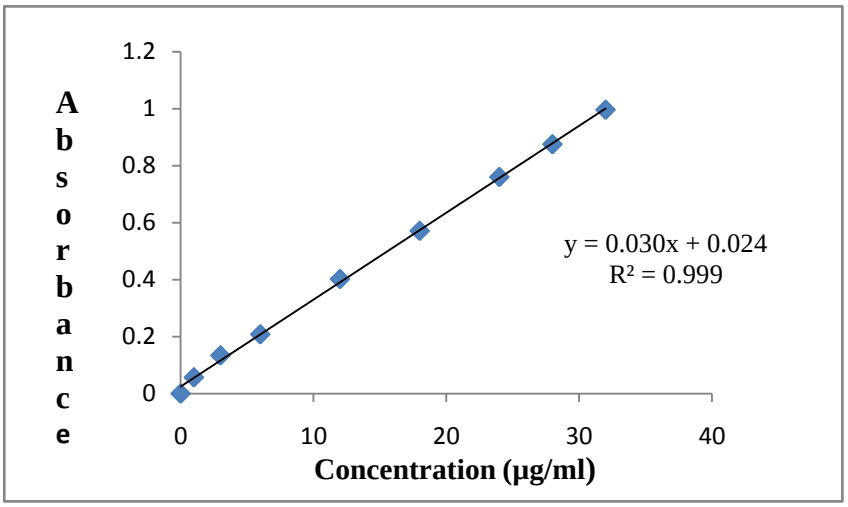

Fig 1 : Standard Graph of Doxofylline in 0.1N HCL

PROPERTIES OF THE POWDER BLEND

All Formulations were evaluated for Compressibility index, Angle of repose and Hausner ratio. The results indicated the pre-compressed blend gas good flow

TABLE 4: FLOW PROPERTIES OF THE FINAL POWDER BLEND

FORMULATION CODE	C.I	ANGLE OF REPOSE	HAUSNER RATIO
FH 1	12.3	28.7º	1.15
FH 2	15.9	29.3º	1.19
FH 3	12.8	27.6º	1.13
FH 4	15.7	28.1º	1.17
FH 5	12.4	28.4º	1.14
FH 6	11.2	27.9º	1.13
FH 7	12.3	26.7º	1.18
FH 8	12.3	28.7º	1.15
FH 9	15.9	29.3º	1.19
FH 10	12.8	27.6º	1.13
FH 11	15.7	28.1º	1.17

EVALUATION OF THE PREPARED TABLETS FOR PHYSICAL PARAMETERS

All Formulations were tested for physical parameter like hardness, thickness, weight variation, friability and drug content. All estimated parameters were found to be within the limits.

TABLE 5: PHYSICAL PARAMETERS OF THE PREPARED FORMULATIONS

FORMULATION CODE	HARDNESS (kg/cm^2)	THICKNESS (mm)	WEIGHT VARIATION (mg)	FRIABILITY (%)	DRUG CONTENT (%)
FH 1	6.50±0.24	7.384±0.05	1094.60±2.12	0.1	97.23
FH 2	6.65±0.18	7.276±0.06	1105.33±1.45	0.27.	99.12
FH 3	6.45±0.37	7.186±0.03	1084.80±1.63	0.19	98.32
FH4	6.80±0.26	7.186±0.04	1095.09±2.43	0.22	99.54
FH 5	6.55±0.54	7.234±0.06	1086.05±4.51	0.18	99.43
FH 6	6.40 ±0.35	7.45 ±0.06	1092.37±3.89	0.21	98.67
FH 7	6.50±0.48	7.38±0.05	1020.09±4.12	0.16	98.97
FH 8	6.45±0.25	7.45±0.25	1022.65±4.20	0.16	98.28
FH9	6.50±0.54	7.50±0.04	1029.15±4.61	0.12	99.43
FH10	6.50±0.50	7.50±0.07	1030.50±4.39	0.1	98.12
FH 11	6.20±0.25	7.38±0.02	1021.25±2.68	0.19	99.48

TABLE 6: *In-vitro* buoyancy Studies.

S.NO	FORMULATION CODE	FLOATING LAG TIME	TOTAL FLOATING TIME
1	FH 1	75 SEC	4hrs
2	FH 2	82 SEC	6hrs
3	FH 3	76 SEC	8hrs
4	FH 4	70 SEC	> 12 hrs
5	FH 5	89 SEC	> 12 hrs
6	FH 6	84 SEC	> 12 hrs
7	FH 7	90 SEC	> 12 hrs
8	FH 8	75 SEC	> 12 hrs
9	FH 9	84 SEC	> 12 hrs
10	FH 10	79 SEC	> 12 hrs
11	FH 11	87 SEC	> 12 hrs

Tablets of all batches had floating lag time below 2 minutes regardless of viscosity and content of HPMC because of evolution of CO_2 resulting from the interaction between sodium bicarbonate and dissolution medium; entrapment of gas inside the hydrated polymeric matrices enables the dosage form to float by lowering the density of the matrices. It was reasoned that as for HPMC content of 10% or more, the particles of HPMC are close enough to permit a faster establishment of the gel layer inside which the CO_2 gas gets entrapped leading to decreased density ultimately leading to floating of the tablet. Total Floating time for the HPMC formulations were above 12 hrs.

***In-vitro* buoyancy Studies of optimized formulation (FH 5)**

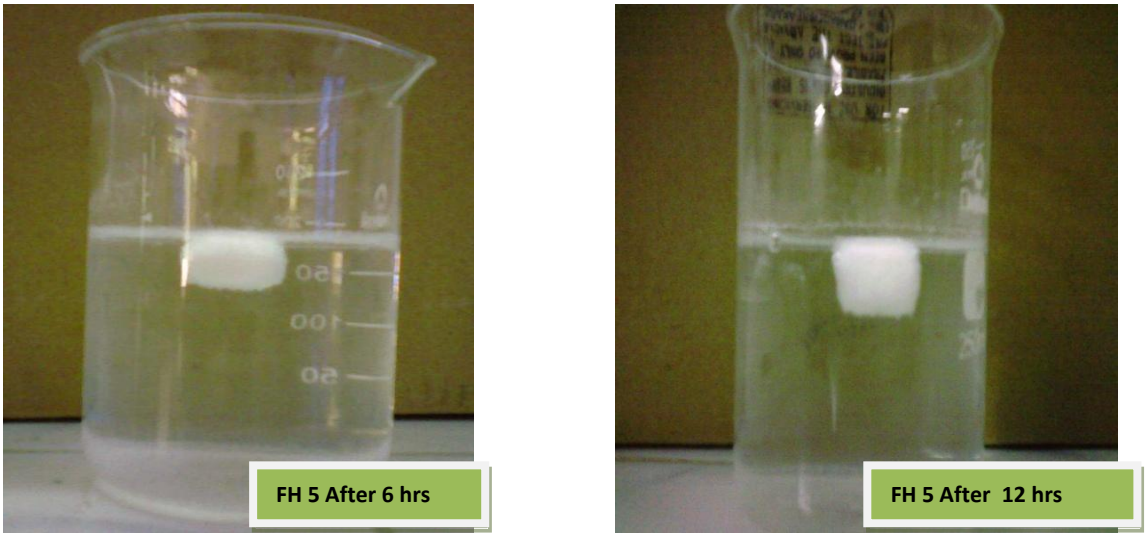

Fig 2 In vitro buoyancy studies of optimized formulation

TABLE 7: CUMULATIVE PERCENT DRUG RELEASE OF DOXOFYLLINE FLOATING TABLETS WITH HPMC K4M POLYMER

TIME (HRS)	CUMULATIVE PERCENT DRUG RELEASE					
	FH 1	FH 2	FH 3	FH 4	FH 5	FH 6
1	97.85±4.38	75.28±2.87	41.39±2.32	36.6±1.82	27.51±3.38	10.25±2.72
2	98.65±3.97	98.75±3.14	72.35±2.79	54.9±2.92	37.03±4.81	15.62±1.45
4	----	97.68±3.54	95.86±1.89	70.24±2.14	57.81±1.96	35.47±1.84
6	----	98.21±2.46	97.85±2.38	85.25±3.81	67.54±3.70	58.38±3.72
8	----	98.27±1.97	98.45±5.78	94.2±4.38	79.89±3.18	69.1±3.49
10	----	97.85±4.58	97.94±4.23	99.3±3.47	86.12±2.54	78.36±4.21
12	----	98.75±4.05	99.45±2.64	99.85±1.75	99.28±2.19	86.57±4.19

TABLE 8: CUMULATIVE PERCENT DRUG RELEASE OF DOXOFYLLINE FLOATING TABLETS WITH CARBOPOL 970 POLYMER

Time (hrs)	Cumulative Percentage Drug Release ±SD				
	FH 7	FH 8	FH 9	FH 10	FH 11
1	41.86±1.57	38.12±1.89	30.31±4.70	18.14±1.26	14.86±0.41
2	56.72±2.31	48.23±5.21	36.78±3.65	29.93±4.17	21.23±3.16
4	72.35±3.56	69.54±3.00	56.22±1.98	42.02±3.14	34.86±1.79
6	77.45±3.70	77.08±1.63	69.92±0.67	55.06±6.52	42.68±1.28
8	84.34±2.84	84.32±2.91	76.90±2.65	64.12±3.90	55.23±2.33
10	98.25±3.84	97.25±1.63	86.37±3.7	77.49±4.70	65.38±2.91
12	97.86±2.14	96.98±4.09	95.49±3.7	81.88±3.47	76.38±2.82

Formulations FH 1 and FH 2 released the drug completely within 2-3 hrs. This was ascertained due to the insufficiency of the polymer to form a rigid gel barrier around the tablet ultimately leading to loss of matrix integrity. Increasing the polymer level (FH 3 formulation) resulted in sustaining the release upto 8-9hrs. FH 4, FH 5, and FH 6 formulations released the drug up to 12 hrs but only FH 5 formulation was found to release the drug according to the predicted theoretical release profile. It shows that increasing concentrations of HPMC K15 M polymer has a retarding effect on the release of Doxofylline from the matrix tablet.

The release from the formulations FH 10 and FH 11 was less than 80% in 12 hrs. The reason expected for this low release is due to incomplete wetting of the matrix by the dissolution medium which was confirmed after 12 hr by scraping off the upper layers of the matrix to reveal dry un-wetted core of the tablets. Among CARBOPOL 970 formulations, FH 8 and FH 9 formulations were found to be in accordance with the Theoretical release profile. But among FH 5 , FH 8 and FH 9 formulations, FH 5 showed greater difference factor (f_1 = 3) and close similarity factor(f_2 =80) when compared with predicted theoretical release profile. Hence FH 5 formulation was chosen as the best optimized formulation

TABLE 9: CORRELEATION- COEFFICIENT (R^2) VALUES OF DIFFERENT KINETIC MODELS

Formulation	R^2				Peppas (n)
	Zero	First	Higuchi	Peppas	
FH 1	0.598	0.567	0.610	0.785	0.393
FH 2	0.612	0.575	0.623	0.815	0.325
FH 3	0.608	0.526	0.663	0.805	0.323
FH 4	0.817	0.809	0.917	0.972	0.408
FH 5	0.927	0.898	0.968	0.995	0.516
FH 6	0.961	0.856	0.942	0.989	0.884
FH 7	0.926	0.861	0.973	0.984	0.337
FH 8	0.931	0.868	0.980	0.987	0.391
FH 9	0.972	0.909	0.994	0.990	0.478
FH 10	0.981	0.912	0.989	0.996	0.602
FH 11	0.991	0.936	0.982	0.992	0.652

It was found out that the optimized formulation FH 5 was best explained by the Higuchi's equation, as the plots showed highest linearity (R^2 = 0.978),followed by Zero order (R^2 = 0.927) and first order(R^2 = 0.898). This explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi's Kinetics).To know the mechanism of drug release the dissolution data was fitted into Korsmeyer - Peppas equation.It also indicated a good linearity (R^2 = 0.995) and the release exponent (n) value was found to be 0.56, which appears to indicate a coupling of the diffusion and erosion mechanism-so called anomalous diffusion-and may indicate that drug release is controlled by more than one process.

CONCLUSION

Sustained release floating tablets of Doxofylline were successfully prepared with hydrophilic polymers like HPMC K4M, CARBOPOL 970. The formulated batches were evaluated for physical parameters, floating properties and dissolution profiles. The physical properties like weight variation and friability of all batches complied with the pharmacopoeial specifications. The drug content of all tablets was in the range of 98 – 102%.From the in vitro dissolution analysis it was found that the batches containing HPMC K4M have less retarding capacity than with batches containing CARBOPOL 970. This is because HPMC K4M is a low viscosity polymer as compared to CARBOPOL 970 polymer. Among HPMC K4M formulations, FH 1 – FH 3 released the drug within 2-6 hrs.This is due to insufficient level of polymer to form a rigid matrix. The optimized formulation among HPMC K4M and CARBOPOL 970 are FH 5 and FH 9. These were chosen because of their close similarity factor with predicted theoretical release profile. FH 5 was the best optimized floating formulation because it released drug completely in 12hrs.It was also observed that the increasing concentration of polymers had a retarding effect on the drug release from the polymer matrices.

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