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Designing and in Vitrocharectarisation of Pulsincap to Promote Floating Drug Delivery System of Dofetilide.

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ABSTRACT
In the present research work floating pulsatile drug delivery system of dofetilide were prepared using various grades of methocel polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various grades of Methocel. The formulation blend was subjected to various pre-formulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Methocel K 4 M were unable to produce desired drug release; they were unable to retard drug release up to 12 hours. Whereas the formulations prepared with Methocel K 15 M retarded the drug release in the concentration of 60 mg (F6)showed required release pattern i.e., retarded the drug release up to 10 hours and showed maximum of 98.97 % in 12 hours with good floating lag time and floating buoyancy time.. The formulations prepared with Methocel K 100 M showed more retardation even after 12 hours they were not shown total drug release. Hence, they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order kinetics.

KEY WORDS: Dofetilide, Methocel K 15 M, Methocel K 4 M, Methocel K 100 M.

Biography: The present research work relates to an Pulsatile drug delivery systems of dofetilide tablet, it was prepared by using the single unit systems i.e,capsular systems. The process in the preparation method of pulsatile drug delivery of dofetilide tablet by having the significant improvement in release kinetics. Dofetilide tablet form of pulsatile drug delivery is prepared by using single capsular method with enhanced bioavailability and improved rate of release kinetics to attain the zero order kinetics.

I. INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. But there are certain conditions which demand release of drug after a lag time. i.e., Chronopharmacotherapy of diseases which shows Circadian rhythms in their pathophysiology. Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions. There are many conditions that demand pulsatile release like

a) Many body functions that follow circadian rhythm. e.g: Secretion of hormones, acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.

b) Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.

c) Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase as this tends to reduce their therapeutic effect.

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d) The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g.: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.
e) Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.
f) The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite, and potential food drug interactions require delayed release of the drug to the extent possible.
All of these conditions demand for a time controlled therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by Pulsatile Drug Delivery Systems.

Diseases Requiring Pulsatile Delivery

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions.

Methods for Pulsatile Drug Delivery

Single unit systems

Capsular system

Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body. e.g.: Pulsincap® system

In this system a water insoluble body containing the drug formulation, system is closed with a swellable hydrogel. Plugged (insoluble but permeable & swellable) at open end. Upon contact with, gastrointestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. Position & dimensions of plug, control lag-time. For rapid release of water insoluble drug effervescent or disintegrating agents are added. Plug material is generally made up of following:

1. Swellable materials coated with but¬ permeable polymer (polymethacrylates).
2. Erodible compressed polymer (HPMC,¬ polyvinyl alcohol).
3. Congealed melted polymer (glyceryl¬ mono oleate).
4. Enzymatically controlled erodible¬ polymer (pectin).

Methodology

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1NHCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.

b) Preparation calibration curve:

100mg of Dofetilide pure drug was dissolved in 100ml of water(stock solution)10ml of solution was taken and make up with100ml of water (100µg/ml).from this 10ml was taken and make up with 100 ml of water (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 2,4,6,8,10,20,30,40,50,60,70,80,90 and 100µg/ml of Dofetilide per ml of solution. The absorbance of the above dilutions was measured at 271 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line. Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compressions of different formulations are given in Table 6.4.The tablets were prepared as per the procedure given below and aim is to prolong the release of Dofetilide. Total weight of the tablet was considered as 300mg.

Procedure:

1) Dofetilide and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

s.no	ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	Dofetilide	125	125	125	125	125	125	125	125	125
2	Methocel K_4M	40	80	100	.....	.....	.....	.....	.....	.....
3	Methocel $K_{15}M$	.....	.....	.....	40	80	100	.....	.....	.....

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4	Methocel $K_{100}M$	.....	.....	.....	.....	.....	.....	40	80	100
5	$NaHCO_3$	30	30	30	30	30	30	30	30	30
6	Mag.sterate	5	5	5	5	5	5	5	5	5
7	Talc	5	5	5	5	5	5	5	5	5

Table 1: Formulation composition for floating tablets

Determination of drug content:

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Meloxicam were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro Buoyancy studies:

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

In vitro drug release studies

Dissolution parameters:

Apparatus -- USP-II, Paddle Method
Dissolution Medium -- 0.1 N HCl
RPM -- 75
Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature -- 37°c $\pm$ 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was continued from 0 to 12 hrs at 75 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 271 nm using UV-spectrophotometer.

II. RESULTS AND DISCUSSION

The present study was aimed to developing gastro retentive floating tablets of Dofetilide using various Methocel polymers. All the formulations were evaluated for physicochemical properties and in vitro drug release studies.

Analytical Method:

Graphs of Dofetilide was taken in Simulated Gastric fluid (pH 1.2) at 271nm.

S	Conc [µg/l]	Abs
1	0	0
2	2	0.172
3	4	0.310
4	6	0.438
5	8	0.563
6	10	0.719
7	10	0.719

Table 3: Observations for graph of Dofetilide in 0.1N HCl (271 nm)

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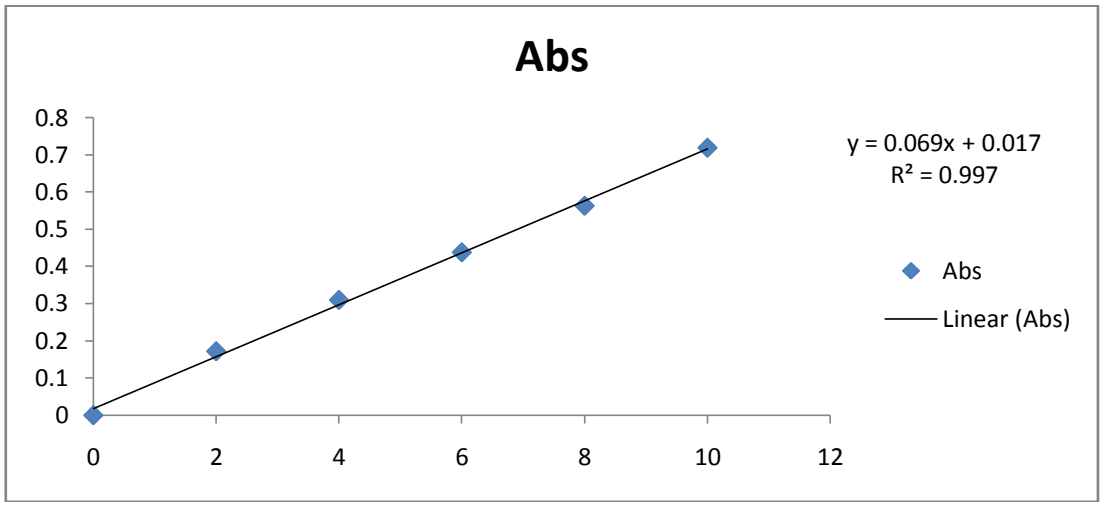

Figure 1: Standard graph of Dofetilide in 0.1N HCl

Pre-formulation parameters of blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43to 0.58 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties.The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties.All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

S.no	Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	Angle of repose	26.01	24.8	22.74	25.33	26.24	26.12	27.08	25.12	25.45
2	Bulk density(gm/ml)	0.79	0.56	0.52	0.54	0.53	0.56	0.58	0.48	0.54
3	Tapped density(gm/ml)	0.57	0.62	0.68	0.64	0.67	0.66	0.69	0.57	0.62
4	Carr's index(%)	16.21	16.87	17.11	17.67	16.92	17.65	16.43	17.97	17.54
5	Hausner's ratio	0.86	0.98	0.64	1.12	1.2	1.06	0.76	1.15	1.17

Table 4: Pre formulation parameters of powder blend

Evaluation of post compression parameters for prepared Tablets

The designed formulation compression coated tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage.

The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

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Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Table 2: Pharmacopoeia specifications for tablet weight variation

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance.Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Optimization of sodium bicarbonate concentration:

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 30mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

S.no	Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	Weight variation(mg)	302.5	305.4	298.6	310.6	309.4	310.7	302.3	301.2	298.3
2	Hardness(kg/cm^2)	3.5	3.2	3.4	3.5	3.4	3.2	3.1	3.3	3.5
3	Friability(% loss)	0.52	0.54	0.51	0.55	0.56	0.45	0.51	0.49	0.55
4	Thickness(nm)	4.8	4.9	4.9	4.9	4.7	4.5	4.4	4.7	4.6
5	Drug content(%)	99.76	99.45	99.34	99.87	99.14	99.56	99.42	99.65	99.12
6	Floating lagtime(min)	4.0	4.2	4.5	4.1	4.0	4.4	4.5	4.6	4.7

Table 5: Invitro quality control parameters for tablet

TIME(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	2.34	2.68	2.89	2.59	12.5	12.87	18.81	19.89	14.21
1	7.04	6.18	9.09	7.65	15.34	16.77	29.02	28.04	18.87
2	8.01	8.59	17.98	15.27	20.54	22.09	35.7	35.43	27.19

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3	20.31	12	28.87	12.73	45.78	33.03	43.32	41.65	35.66
4	28.15	23.96	38.77	20.3	57.55	47.15	49.25	47.18	43.32
5	32.17	31.27	46.78	32.57	61.6	55.38	55.28	53.81	51.06
6	41.07	40.79	57.77	40.03	67.63	60.19	60.92	58.89	57.13
7	49.03	49.33	68.98	55.62	70.2	73.38	66.08	64.53	63.63
8	56.5	56.92	75.43	61.35	75.76	80.27	70.44	69.43	69.71
9	69.15	69.06	81.34	72.53	81.6	85.44	81.9	73.44	72.34
10	73.39	78.12	85.67	79.87	83.82	87.24	85.27	76.89	78.54
11	77.87	82.34	88.93	82.34	87.88	91.56	89.56	79.98	83.27
12	81.78	85.67	92.67	89.03	90.92	97.47	92.33	83.98	89.02

Table 6:Dissolution Data of Dofetilide Tablets

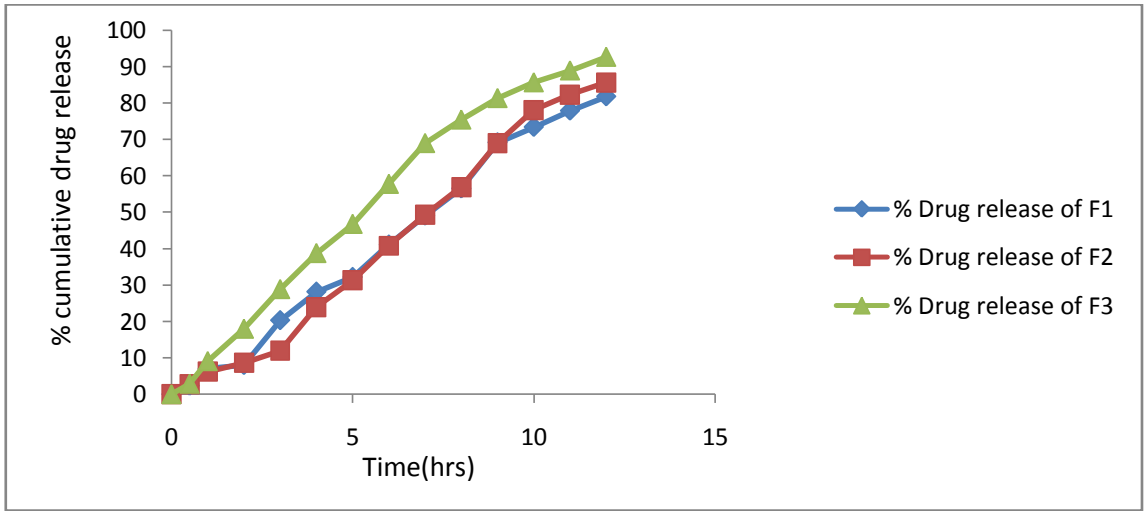

Fig 2: Dissolution profile of DOFETILIDE floating tablets (F1, F2, F3 formulations).

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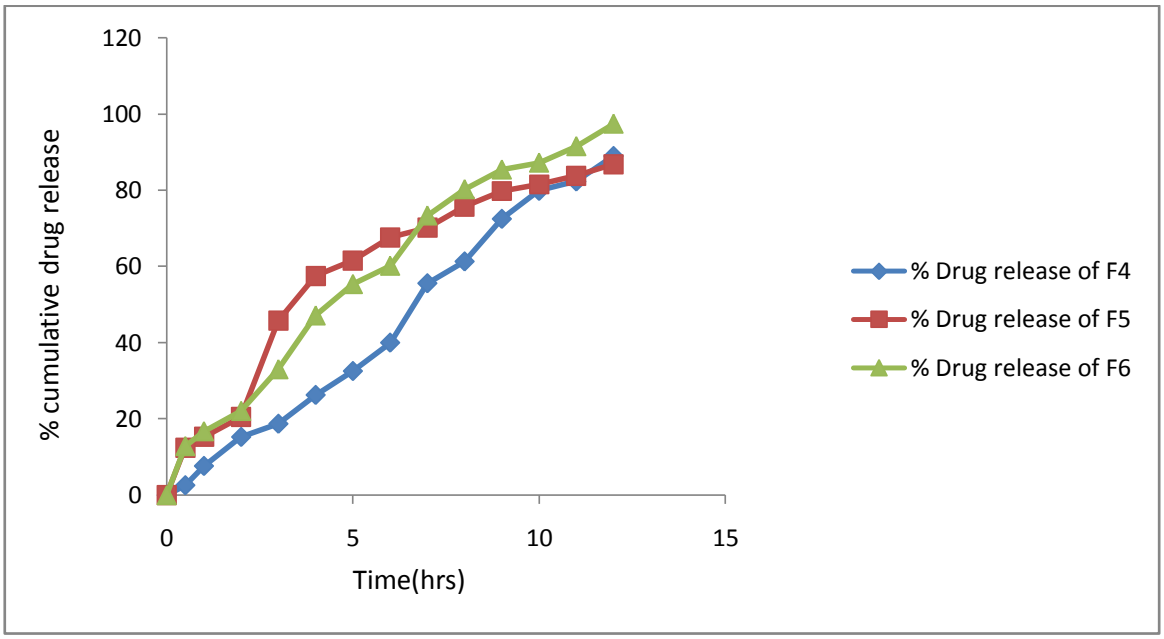

Fig 3: Dissolution profile of Dofetilide HCl floating tablets (F4, F5, F6 formulations).

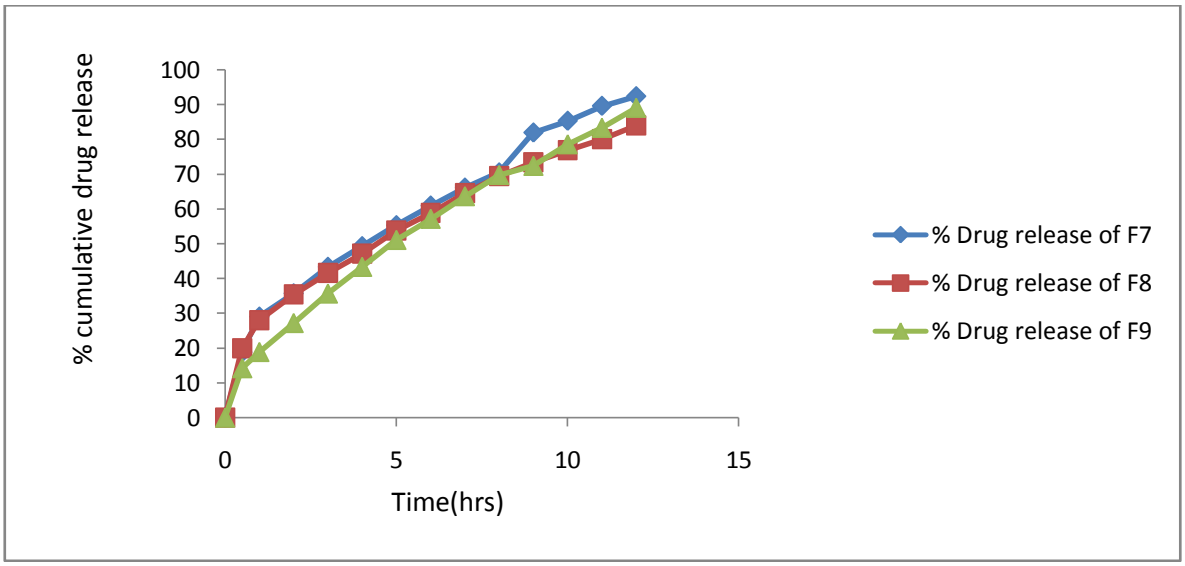

Fig 4: Invitro Dissolution profile of Dofetilide floating tablets (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with Methocel K 4 M as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Whereas, the formulations prepared with Methocel K 15 M retarded the drug release in the concentration of 60 mg (F6)showed required release pattern i.e., retarded the drug release up to 10 hours and showed maximum of 98.97 % in 12 hours with good floating lag time and floating buoyancy time.

The formulations prepared with Methocel K 100 M showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

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Cumulative (%) release	Time (t)	Root (t)	Log (%) release	Log (t)	Log (%) remain
	0	0			2.000
12.87	0.5	0	1.110	0	1.940
16.77	1	1.000	1.225	0.000	1.920
22.09	2	1.414	1.344	0.301	1.892
33.03	3	1.732	1.519	0.477	1.826
43.25	4	2.000	1.673	0.602	1.723
55.38	5	2.236	1.743	0.699	1.650
60.19	6	2.449	1.780	0.778	1.600
73.38	7	2.646	1.866	0.845	1.425
80.27	8	2.828	1.905	0.903	1.295
85.44	9	3.000	1.932	0.954	1.163
87.24	10	3.162	1.941	1.000	1.106
91.56	11	3.317	1.962	1.041	0.926
97.47	12	3.464	1.989	1.079	0.403

Table 7: Release kinetics data for optimised formulation

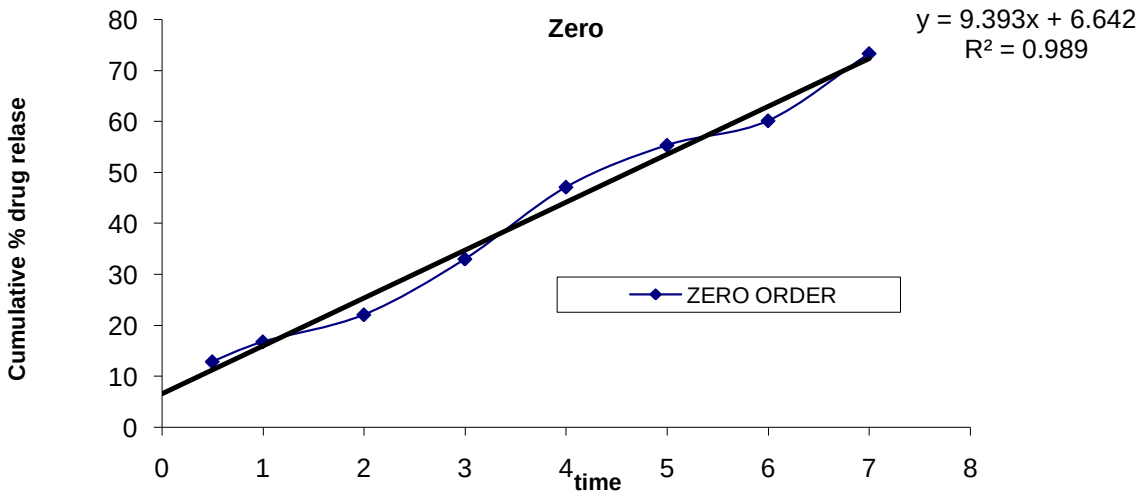

Fig 5 : Zero order release kinetics graph

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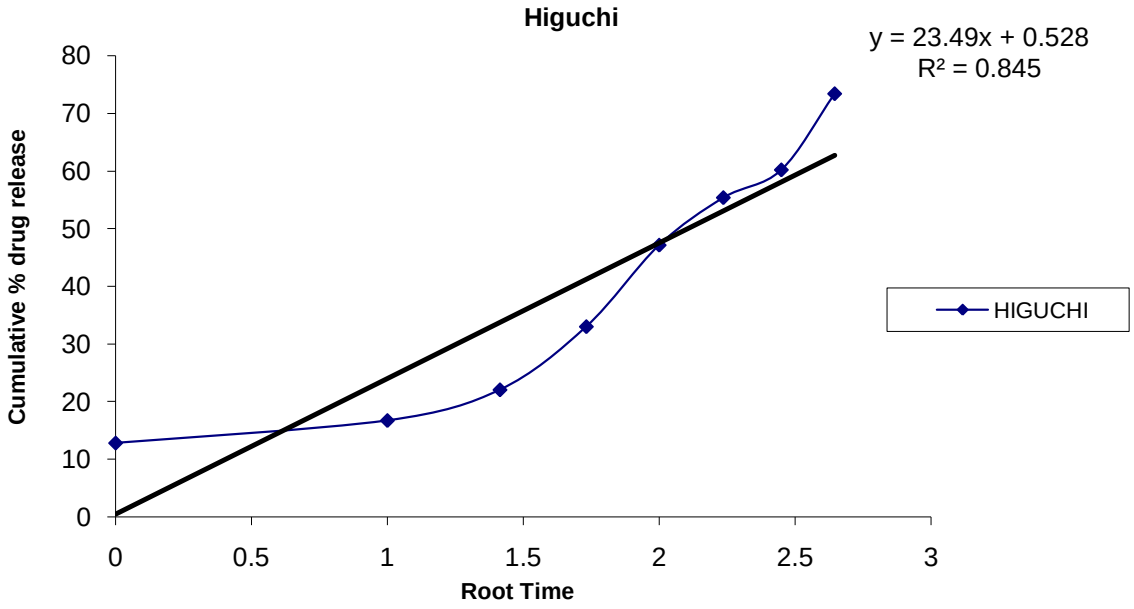

Fig 6: Higuchi release kinetics graph

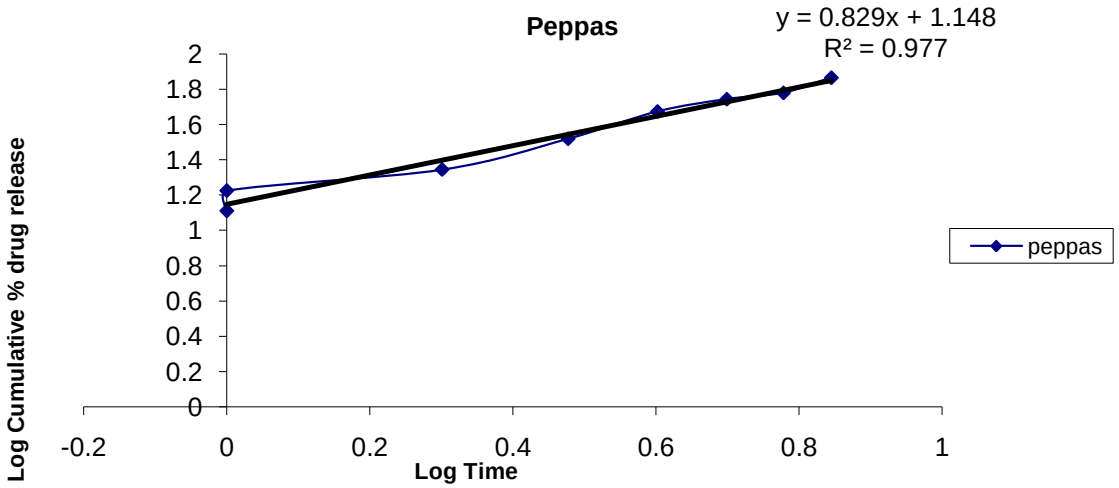

Fig 7: Kars mayer peppas graph

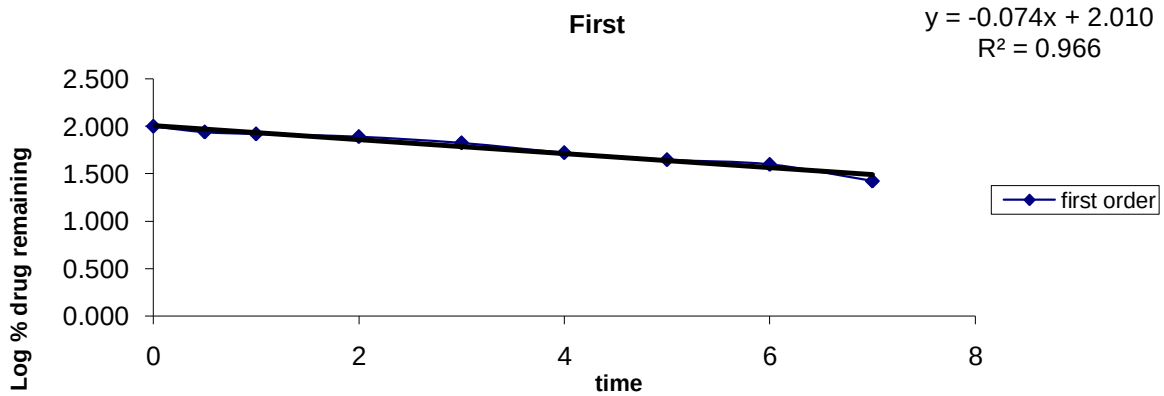

Fig 8: First order release kinetics graph

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From the above graphs it was evident that the formulation F6 was followed zero order kinetics.

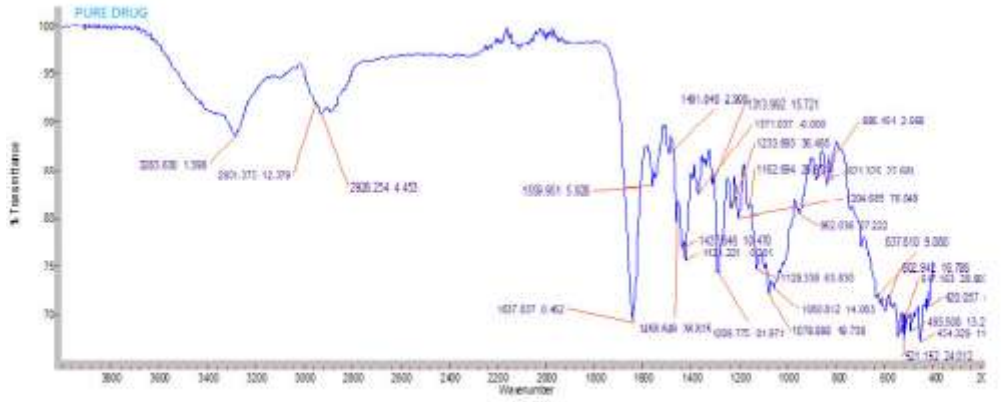

Fig 9: FTIR spectrum of pure drug

Fig 10: FTIR spectrum of optimized formulation

III. CONCLUSION

In the present research work floating pulsatile drug delivery system of dofetilide were prepared using various grades of methocel polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various grades of Methocel. The formulation blend was subjected to various preformulation studies,flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using MethocelK4 M were unable to produce desired drug release,they were unable to retard drug release up to 12 hours. Whereas the formulations prepared with Methocel K15M retarded the drug release in the concentration of 60mg(F6) showed required release pattern i.e., retarded the drug release up to 10 hours and showed maximum of 98.97 % in 12 hours with good floating lag time and floating buoyancy time. The formulations prepared with Methocel K 100 M showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered. The optimized formulation

dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order kinetics.

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