World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 6, Issue 8, 2017 ISSN: 2319-5622 USA CODEN: JPROK3

Research Article

DOFETILIDE FORMULATION AND *IN-VITRO* EVALUATION BY CHRONOMODULATED DRUG DELIVERY

Kousar Begum *, C. Aditya, A. Narasimha Charan, T. Vinay Kumar, Dr. B. Chandra Sekhara Rao

Faculty of Pharmacy, RGRSCP, Secunderabad, Telangana, India.

Received on: 23-07-2017; Revised and Accepted on: 04-08-2017

ABSTRACT

Oral controlled drug delivery systems are most conventional and preferable route of administration for most of the drugs. In the present research work is on pulsatile drug delivery system of dofetilite by using various hydrophillic polymers has done. To increase the bioavailability and sustained action of Dofetilide, there are different grades of polymers like HPMC K $_4$ M and HPMC K $_{100}$ M and HPMC K$_{15}$ M are used in different formulations. Effervescent floating delivery systems were prepared by varying in the polymer as well as in the sodium bicarbonate concentration. They were total 9 formulations were prepared by direct compression method and evaluated for both preformulation and post formulation studies. Out of all the formulation prepared with HPMC K$_{15}$ M retarded the drug release up to 12 hours in the concentration of 75 mg (F$_3$). The optimized formulation dissolution data was subjected to first order release kinetics, from the release kinetics data (99.69 %.) it was evident that the formulation followed First order mechanism of drug release.

Keywords: *Dofetilide, Pre-Formulation studies, Gastro Retentive Floating Drug Delivery, First order kinetics, HPMCK $_{15}$ M.*

INTRODUCTION

The oral drug delivery system one of the most satisfactory and secure means for administration of the drugs because of its appropriateness and simplicity of administration. Conventional dosage form can partially achieve the goal of delivering the therapeutic response over the time of dose interval. Recent technological development and advances in oral drug delivery has guided the pharmaceutical industry towards the improvement of dosage forms. Novel drug delivery system (NDDS) is much vital. This system has remedial efficiency, little prevalence of toxicity and better stability profile [1].

The design of oral controlled drug delivery systems (CDDS) should primarily aimed at achieving more Predictable and increased bioavailability of drugs. The gastric emptying process can vary from a few minutes to 12 hrs. This mainly lead to unpredictable time for peak plasma levels & bioavailability. Furthermore, the relative gastric emptying time (GET) this is normally 2 to 3 hrs. Through the major absorption zone (stomach or upper part of intestine), and can result in incomplete drug released from the DDS leading to diminished efficacy of the administered dose. Therefore placing of DDS in specific region of the GIT offers numerous advantages. specially the drugs having narrow absorption window in GIT, primary absorption in the stomach, stability problem in the intestine, poor solubility at alkaline pH, local activity in stomach, and property to degrade in colon [2].

Nowadays are mainly focus on prevention of drug wastage, right place and right time of the formulated drug of delivery system. Chronomodulated drug delivery system is the most efficient system in delivery the active pharmaceutical ingredient (API). In case in sustained release formulation continuously taking of the drug to body it may lead to adverse drug reaction.

Chronomodulated drug delivery (CDDS) or Pulsatile drug delivery system (PDDS) is the actually time-delayed or time controlled drug delivery system. Chronomodulated drug delivery system controls the lag-time of some factors like enzymatic activity, GI-Motility and pH etc. Chronopharmaceutics denoted as temporal changes in the ADME process. In which systems are fabricated accordingly to the circadian rhythms of the human body [3].

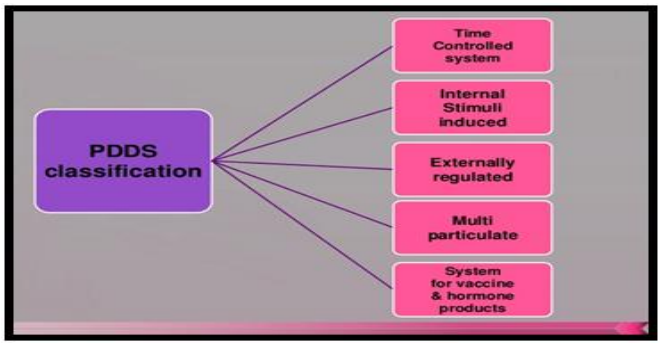

Fig. 1: Uncontrolled diabetes can lead to nerve damage [4]

Formulation Consideration: Different approaches of pulsatile system are broadly divided as follows:

Time controlled: In time controlled drug delivery system, drug is released in pulsatile manner after specific time interval in order to coincide the drug with proper site, thus mimic the circadian rhythm.

a. Pulsatile Delivery by Solubilisation or Erosion of layer
b. Pulsatile Delivery by Rupture of Membrane
c. Capsule Shaped Pulsatile Drug Delivery System
d. Pulsatile System Based On Osmosis [5].

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged

***Corresponding author:**
Kousar Begum,
Faculty of Pharmacy,
RGR Siddhanthi College of Pharmacy,
Secunderabad, Telangana, INDIA.
**E-Mail: kousar.ceutics@gmail.com*

period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal . Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. Table 1 enlists examples of various drugs formulated as different forms of FDDS [6].

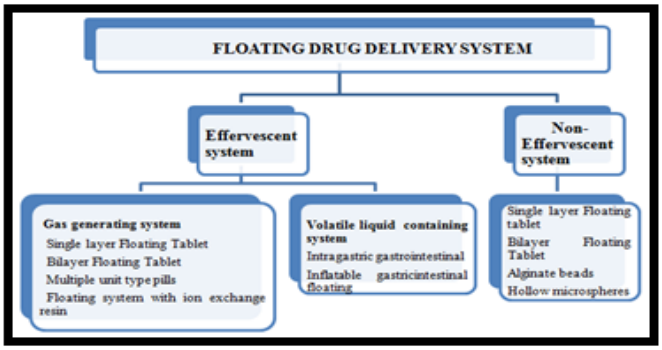

Fig. 2: Uncontrolled diabetes can lead to nerve damage [7]

Major Merits of FDDS:

- Drugs with considerably short half life can be administered in this manner.
- The duration of treatment through a single dose, which releases the an active ingredient over an extended period of time.

Major De-Merit of FDDS:

- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems [8].

Aim:

To formulate and evaluate the Dofetilide controlled release tablets for pulsatile drug delivery system by using various grades of HPMC Polymers.

Objectives:

- ✓ To study the effect of Drug polymer ratio or concentration of polymer on drug release.
- ✓ To study the effect of polymer, polymer grades on the parameters like duration of buoyancy
- ✓ Formulate Dofetilide effervescent floating tablets with HPMC K 4 M, HPMC K 15 M, HPMC K 100 M.
- ✓ Determination of effect of sodium bicarbonate concentration on floating lag time and drug release.
- ✓ To determine the kinetics and mechanism of drug release, *in-vitro* drug release studies
- ✓ Construction of calibration curve of Dofetilide in 0.1 N HCl.
- ✓ To evaluate prepared formulations for floating lag time and total floating time.
- ✓ To evaluate prepared core tablets for various preformulation parameters
- ✓ Optimization of the best batch of tablets based on the in-vitro release data.

MATERIALS AND METHODS

Table No. 1: List of Materials Used

Name of the material	Source
DOFETILIDE	AURABINDO PHARMA PVT LTD
HPMC K_4 M	Merck Specialities Pvt Ltd, Mumbai, India
HPMC K_{15} M	Merck Specialities Pvt Ltd, Mumbai, India
HPMC K_{100} M	Merck Specialities Pvt Ltd, Mumbai, India
Sodium bicarbonate	Merck Specialities Pvt Ltd, Mumbai, India
Micro crystalline cellulose	Merck Specialities Pvt Ltd, Mumbai, India
Talc	Merck Specialities Pvt Ltd, Mumbai, India

Table No. 2: List of Equipment used

Name of the Equipment	Manufacturer
Weighing Balance	Wensar
Tablet Compression Machine (Multistation)	Karnavati.
Hardness tester	Monsanto hardness tester
Vernier calipers	Mitutoyo, Japan.
Roche Friabilator	Labindia, Mumbai, India
Dissolution Apparatus	Labindia, Mumbai, India
UV-Visible Spectrophotometer	Labindia, Mumbai, India
pH meter	Labindia, Mumbai, India
FT-IR Spectrophotometer	Per kin Elmer, United States of America.

Methodology:

Analytical method development:

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl 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.

Drug – Excipient compatibility studies:

a) Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

b) Pre-formulation parameters of powders:

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia [9].

1. Angle of repose:

$$\text{Tan } \theta = h / r$$

Tan θ= Angle of repose, h = Height of the cone, r = Radius of the cone base

Table No. 3: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

2. Bulk density:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample, V_o = apparent volume of powder

3. Tapped density:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density, M = Weight of sample, V= Tapped volume of powder

4. Measures of powder compressibility by Carr's Index:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density , Tap = Tapped Density

Table No. 4: Carr's Index value (as per USP) [10]

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Table No. 5: Formulation development of Tablets: Formulation composition for floating tablets

Formulation No.	Dofetilide	HPMC $K_{15}M$	HPMC K_4M	HPMC $K_{100}M$	$NaHCO_3$	Talc	MCC pH102
F1	100	25	-----	-----	30	5	QS
F2	100	50	-----	-----	20	5	QS
F3	**100**	**75**	**----**	**-----**	**10**	**5**	**QS**
F4	100	-----	25	-----	30	5	QS
F5	100	-----	50	----	20	5	QS
F6	100	-----	75	-----	10	5	QS
F7	100	-----	-----	25	30	5	QS
F8	100	-----	-----	50	20	5	QS
F9	100	-----	-----	75	10	5	QS

All the quantities were in mg, total weight is 200 mg.

All the formulations were prepared by direct compression. The compressions of different formulations are given in Table 5. The tablets were prepared as per the procedure given below. Total weight of the tablet was considered as 200mg.

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.

Evaluation of post compression parameters for prepared Tablets:

1. Weight variation test:

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

2. Hardness
3. Thickness
4. Friability

$$\text{\% Friability} = [(W1-W2) / W] \times 100$$

Where, W1 = Initial weight of three tablets, W2 = Weight of the three tablets after testing.

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 Dofetilide 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 ± 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 0.1N 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 ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours 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 [11].

Application of Release Rate Kinetics to Dissolution Data:

Zero order release rate kinetics by $F = K_o t$

Where, 'F' is the drug release at time 't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics by Log (100-F) = kt

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model by $F = k t_{1/2}$

Where, 'k' is the Higuchi constant. In Higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer-Peppas release model by $M_t/ M_\infty = K t^n$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant and 'n' is the diffusional exponent which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model by $(100-Q_t)^{1/3} = 100^{1/3} - K_{HC}.t$

Where, k is the Hixson-Crowell rate constant [12].

RESULTS AND DISCUSSIONS

Analytical Method:

Graphs of Dofetilide was taken in Simulated Gastric fluid (pH 1.2) at 271 nm. Observations for graph of Dofetilide in 0.1N HCl (271 nm).

Table No. 6: Linearity range for Dofetilide in 0.1N HCl

Concentration [µg/ml]	Absorption
0	0
2	0.172
4	0.310
6	0.438
8	0.563
10	0.719

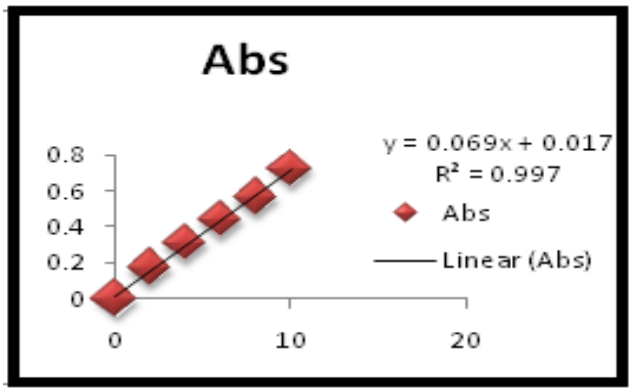

Fig. 3: Standard graph of Dofetilide in 0.1N HCl

FTIR spectrum of pure drug:

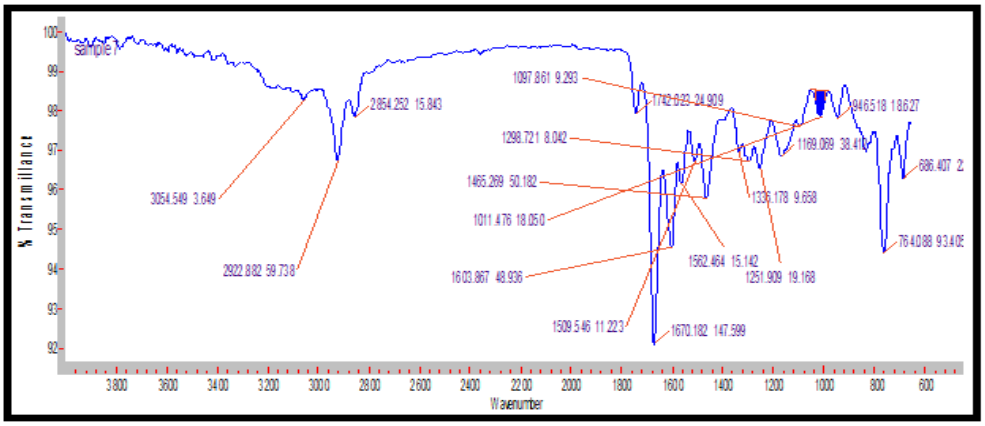

Fig. 4: FTIR spectrum of optimized formulation

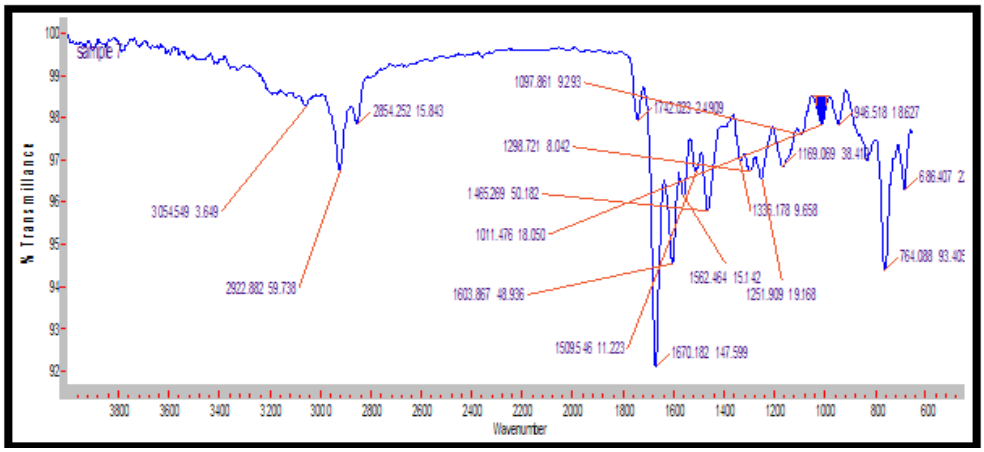

Fig. 5: Flow properties of formulation

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 0.43±0.07 to 0.58±0.06 (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.

Table No. 7: Pre-formulation parameters of powder blend

Z	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

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.

Table No. 8: *In-vitro* quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)
F1	302.5	3.5	0.52	4.8	99.76	4.0
F2	305.4	3.2	0.54	4.9	99.45	4.2
F3	298.6	3.4	0.51	4.9	99.34	4.5
F4	310.6	3.5	0.55	4.9	99.87	4.1
F5	309.4	3.4	0.56	4.7	99.14	4.0
F6	310.7	3.2	0.45	4.5	98.56	4.4
F7	302.3	3.1	0.51	4.4	98.42	4.5
F8	301.2	3.3	0.49	4.7	99.65	4.6
F9	298.3	3.5	0.55	4.6	99.12	4.7

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table No. 9: *In-Vitro* Drug Release Studies: Dissolution Data of Dofetilide Tablets

TIME (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	10.21	15.65	17.29	15.65	14.56	12.32	18.76	18.31	13.44
1	24.55	21.34	20.76	19.03	22.13	19.88	28.21	26.09	21.87
2	32.24	29.76	25.23	22.05	29.01	36.35	34.03	33.21	29.09
3	44.56	37.87	35.66	29.88	39.32	43.56	41.08	42.45	36.55
4	49.25	42.61	45.32	43.54	42.45	49.34	49.21	47.21	47.32
5	54.45	49.37	56.22	49.04	49.56	56.65	54.39	53.55	55.64
6	59.39	57.45	59.34	52.46	52.44	63.54	62.05	62.34	59.21
7	62.65	62.76	64.21	61.34	59.32	69.76	68.55	71.09	64.43
8	68.99	69.32	71.34	73.45	64.56	78.32	79.01	79.87	67.88
9	72.83	77.65	78.28	81.07	72.39	83.43	85.12	83.42	77.91
10	79.65	82.67	87.03	85.78	79.65	86.65	90.55	89.54	89.19
11	81.23	86.98	95.72	89.37	83.42	89.65	93.07	94.76	95.76
12	84.62	92.55	99.69	92.45	88.03	93.43	94.54	96.07	97.65

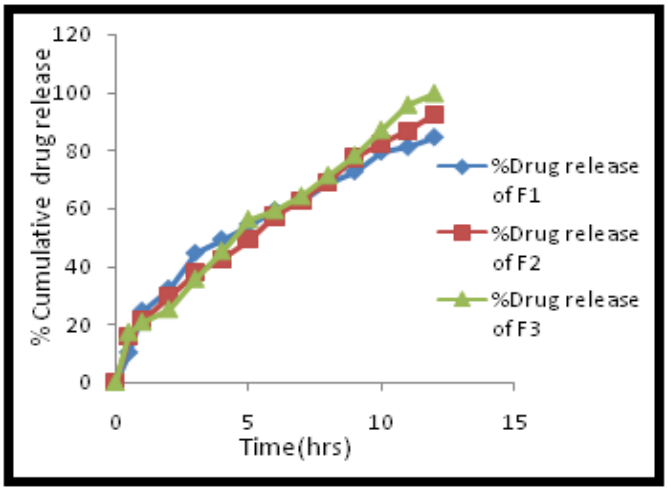

Fig. 6: Dissolution profile of Dofetilide floating tablets (F1, F2, F3 formulations)

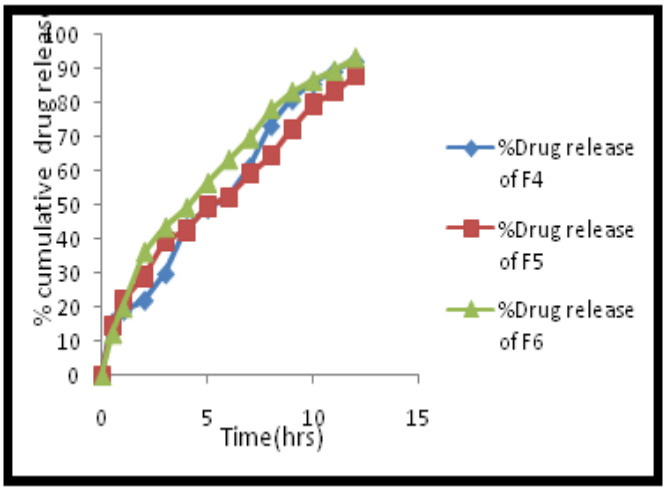

Fig. 7: Dissolution profile of Dofetilide HCl floating tablets (F4, F5, F6 formulations)

From the dissolution data it was evident that the formulations prepared with HPMC 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 HPMC K 15 M retarded the drug release in the concentration of 75 mg (F3) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.69 % in 12 hours with good floating lag time and floating buoyancy time.

The formulations prepared with HPMC 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.

Table No. 10: Release kinetics data for optimised formulation

Cumulative (%) Release Q	Time (T)	Root (T)	LOG (%) Release	LOG (T)	LOG (%) Remain
0	0	0			2.000
17.29	0.5	0.707	1.238	-0.301	1.918
20.76	1	1.000	1.317	0.000	1.899
25.23	2	1.414	1.402	0.301	1.874
35.66	3	1.732	1.552	0.477	1.808
45.32	4	2.000	1.656	0.602	1.738
56.22	5	2.236	1.750	0.699	1.641
59.34	6	2.449	1.773	0.778	1.609
64.21	7	2.646	1.808	0.845	1.554
71.34	8	2.828	1.853	0.903	1.457
78.28	9	3.000	1.894	0.954	1.337
87.03	10	3.162	1.940	1.000	1.113
95.72	11	3.317	1.981	1.041	0.631
99.69	12	3.464	1.999	1.079	-0.509

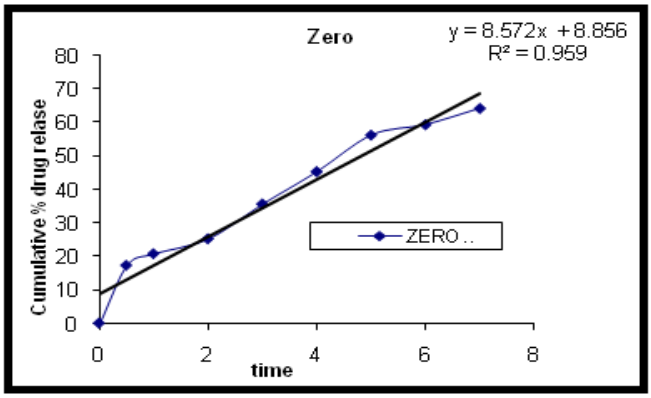

Fig. 8: Zero order release kinetics graph

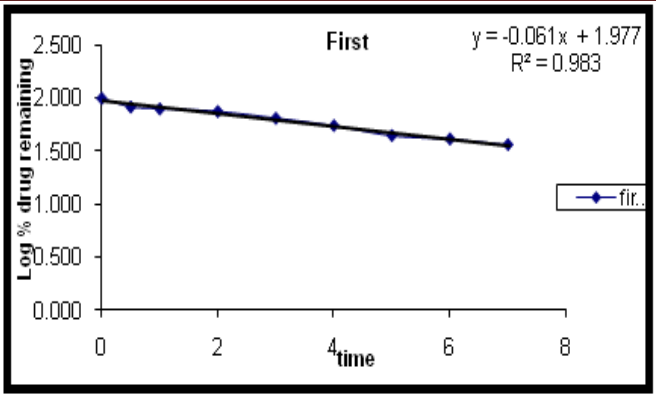

Fig. 9: First order release kinetics graph

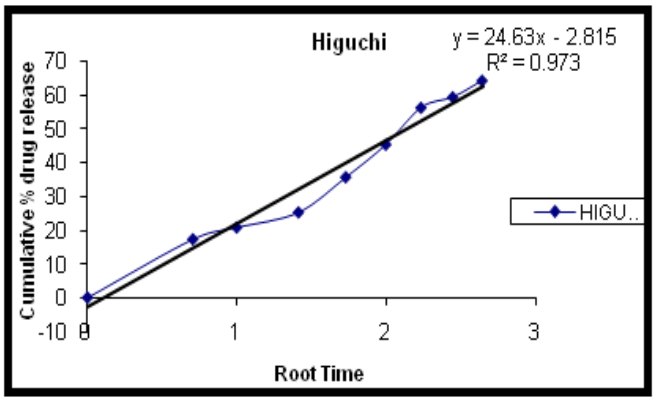

Fig. 10: Higuchi release kinetics graph

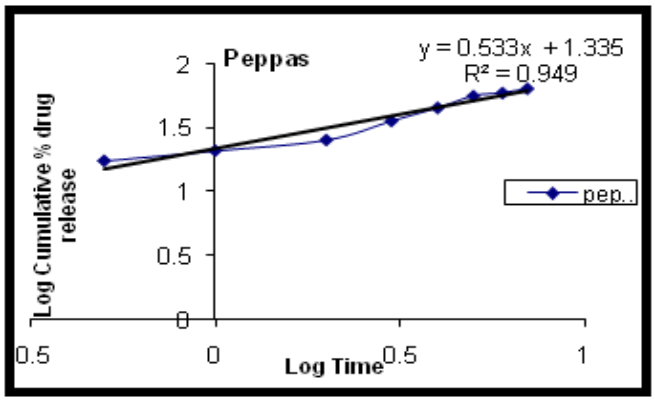

Fig. 11: Korsmeyer-Peppas graph

CONCLUSION

By the analytical methods of Dofetilide 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 HPMC. 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 of HPMC K_4 M and HPMC K_{100} M were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulation prepared with HPMC K_{15} M retarded the drug release up to 12 hours in the concentration of 75 mg (F_3). With the study of drug release kinetics I conclude that, F_3 is the optimized formulation as it retards upto 12 hrs and releases maximum drug 99.69% and it follows first order kinetics.

REFERENCES:

1. Muhammad Zaman et al. Oral controlled release drug delivery system and Characterization of oral tablets; A review. PJPR **2016**;67-76.
2. Chikhalikar SS. et al. Floating Drug Delivery System – An Approach tooral Controlled Drug Delivery. IJPRIF **2012**;4(4):1812-1826.
3. Jagadesh Kumar Yadav et al. Time Controlled Chronomodulated Drug Delivery System - A Critical Review. IJIPR **2014**;5(2):405-409.
4. https://image.slidesharecdn.com/pulsatiledrugdeliverysystem-150215110749-conversion-gate02/95/pulsatile-drug-delivery-system-10-638.jpg?Cb=1442670306.
5. Ganesh Rasve et al. Pulsatile Drug Delivery System: Current Scenario. IJPBS **2011**;2(3):332-343.
6. Vishal Bhardwaj et al. Floating Drug Delivery System: A Review. Pharmacophore **2013**;4(1):26-38.
7. http://pharmachitchat.com/wp-content/uploads/2015/05/ba395-pharmatutor-art-2129-2.png.
8. Hemant Maheta etal., an overview on floating drug delivery system, **2017,** http://www.pharmachitchat.com/an-overview-on-floating-drug-delivery-system.
9. P.sindhuri et al. Formulation and invitro evaluation of colon targeted drug delivery of piroxicam tablets. IJUPBS **2017**;6(3):16-29.
10. Subrahmanyam C.V.S, Textbook of physical pharmaceutics, 2nd ed. New Delhi: Vallabh Prakashan. **2001**;253-261.
11. Leon Lachman, Herbert A. Liberman, the Theory and Practice of Industrial Pharmacy. 293-302.
12. Chein Y.W, Novel Drug Delivery Systems, 2nd ed.: Marcel Dekker; New York: **1992**; P.4-300.

How to cite this article:

Kousar Begum et al. DOFETILIDE FORMULATION AND *IN-VITRO* EVALUATION BY CHRONOMODULATED DRUG DELIVERY. J Pharm F 2017;6(8):108-114.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil