JOURNAL OF DRUG DELIVERY RESEARCH

eISSN 2319-1074

RESEARCH ARTICLE

FORMULATION AND INVITRO EVALUATION OF NIFEDIPINE EFFERVESCENT FLOATING MATRIX TABLETS

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Publication history: Received on 27.2.2017 , Published online on 22.3.2017

ABSTRACT

In the present research work gastro retentive floating matrix formulation of Nifedipine by using various hydrophilic polymers were developed. The formulation was developed by using different concentrations of polymers of Gum cyamposis, xanthan gum and sodium alginate as polymeric substances. The formulation blend was subjected to various preformualation 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 gum cyamposis as polymer were retarded the drug release up to desired time period i.e., 12 hours in the concentration of 60 mg. whereas in low concentrations the polymer was unable to produce the desired action. (F3 Formulation, 99.36% Drug release). The formulations prepared with sodium alginate were also retarded the drug release for more than 12 hours. 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 mechanism of drug release.

Keywords: Nifedipine, Hydrophilic polymers, Floating tablets.

INTRODUCTION

Oral delivery of drugs is the most preferable route of drug delivery. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient compliance and flexibility in formulation and cost effective manufacturing process[1]. Conventional immediate oral dosage forms provides a specific drug concentration in the systemic circulation with limited control over drug delivery. Controlled-release drug delivery systems provide drug release at a predetermined, predictable rate and optimize the therapeutic effect of a drug by controlling its release in the body with lower and less frequent doses[2].

A major constraint in oral controlled drug delivery is that most of the drug candidates are not absorbed uniformly throughout the gastrointestinal tract. Some drugs are absorbed only in a particular region of the GIT [3] or are absorbed to a different extent in various segments of the GIT and are said to have an absorption window which identifies the primary region of absorption of the drug in the GIT because of physiological, physicochemical or biochemical factors[4].

Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems. Gastro retentive drug delivery system can improve controlled delivery of drugs with an

eISSN 2319-1074

absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring optimal bioavailability[5].

MATERIALS AND METHODS

Materials

Nifedipine was obtained as a gift sample from Sura Labs, Hyderabad, India. Gum cyamopsis, Xanthan gum, Sodium alginate, Sodium bicarbonate, Magnesium stearate, Micro crystalline cellulose and Talc were purchased from Merck Specialities Pvt Ltd, Mumbai, India. All other ingredients were of laboratory grade.

Methods

Preparation of Losartan Potassium floating tablets

All the formulations (Table 1) were prepared by direct compression. Nifedipine and all other ingredients except lubricant and glidant were individually passed through sieve no ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc and Magnesium stearate. Then compression was carried out using 10 mm flat-faced circular punches on rotary compression machine. Hardness was maintained between 3-6 Kg/cm^2.

Table 1: Formulation composition for floating tablets

Formulation Code	Nifedipine	Gum Cyamopsis	Xanthan gum	Sodium alginate	$NaHCO_3$	Mag. Stearate	Talc	MCC pH 102	Total weight
F1	20	20	-----	-----	60	4	4	QS	200
F2	20	40	-----	-----	60	4	4	QS	200
F3	20	60	-----	-----	60	4	4	QS	200
F4	20	-----	20	-----	60	4	4	QS	200
F5	20	-----	40	-----	60	4	4	QS	200
F6	20	-----	60	-----	60	4	4	QS	200
F7	20	-----	-----	20	60	4	4	QS	200
F8	20	-----	-----	40	60	4	4	QS	200
F9	20	-----	-----	60	60	4	4	QS	200

All the quantities were in mg

EVALUATION

Angle of repose

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained .Diameter of heap, D, was measured .The repose angle (**θ)** was calculated by following formula (Ansel. 2006).

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$$Tan\theta = \frac{2h}{D}$$

Carr's index and Hausner ratio

Tapped density was determined by placing a graduated cylinder containing a known mass of the prepared granules on a mechanical tapping apparatus, which was operated for a fixed number of taps until the bed volume reached to a minimum. Bulk density was determined by pouring weighed quantity pre- sieved granules into a graduated cylinder and measuring the volume. The Carr's index (CI) and Hausner's ratio (HR) were calculated using following formula[6].

$$CI = \frac{TD - BD}{TD} X100$$

$$HR = \frac{TD}{BD}$$

Whereas CI= Carr's index
TD= Tapped density
BD= Bulk density
HR= Hausner's ratio

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 determining 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[7].

$$\%\, Deviation = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} x100$$

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[7].

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for tablets is calculated.

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

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weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\%\ Friability = \frac{initial\ weight\ of\ tablets - final\ weight\ of\ tablets}{initial\ weight\ of\ tablets} x100$$

Determination of drug content:

Floating tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Nifedipine 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[8].

In vitro Buoyancy studies:

The in vitro buoyancy was determined by floating lag time, and total floating time[9]. 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**

The release of drug from floating tablets was determined using *United States Pharmacopoeia* (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl, at 37 ± 0.5°C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at different time intervals and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 237 nm using UV-spectrophotometer[10,11].

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[10].

Zero order release rate kinetics: To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = k_o t$$

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: The release rate data are fitted to the following equation

$$Log(100 - F) = kt$$

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: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

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$$F = kt^{1/2}$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$Mt/M\infty = kt^n$$

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 I I 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:

$$(100 - Qt)^{\frac{1}{3}} = 100^{\frac{1}{3}} - k.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

RESULTS AND DISCUSSIONS

Gastroretentive tablets of Nifedipine were developed to increase the gastric retention time of drug, so that they can be retained in stomach for longer time. The floating tablets of Nifedipine were made using gel forming polymers such as Gum cyamopsis, Xanthan gum, Sodium alginate (Table-1). They are known for improving the buoyancy characteristics and drug release.

All the Tablets were prepared by effervescent approach. Sodium bi- carbonate was added as a gas generating agent.

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 0.35 ± 0.08 to 0.47 ± 0.53 (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 0.41 ± 0.14 to 0.53 ± 0.51 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 14.5 ± 0.43 to 18.36 ± 0.34 which show that the powder has good flow properties. All the formulations have shown the hausner's ratio ranging between 0 to 1.25 indicating the powder has good flow properties. (Table 2).

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits Table 3).

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From the dissolution data it was evident that the formulations prepared with gum cyamposis as polymer were retarded the drug release up to desired time period i.e., 12 hours in the concentration of 60 mg. whereas in low concentrations the polymer was unable to produce the desired action. (F3 Formulation 99.36% Drug release). The formulations prepared with sodium alginate retarded the drug release in more than 12 hours in higher concentrations. In lower concentrations the polymer was unable to retard the drug release. The formulations prepared with xanthan gum showed very less retardation capacity hence they were not considered. (Table 4) (Fig 1).

Table 2: Preformulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped densit (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.19 ± 0.12	0.35 ± 0.08	0.41 ± 0.14	14.63 ± 0.53	1.17 ± 0.02
F2	27.32 ± 0.25	0.37 ± 0.12	0.45 ± 0.35	17.77 ± 0.44	1.21 ±0.03
F3	25.43 ± 0.31	0.40 ± 0.34	0.48 ± 0.43	16.66 ± 0.37	1.2 ± 0.04
F4	28.17 ± 0.43	0.46 ± 0.53	0.53 ± 0.51	13.02 ± 0.25	1.15 ± 0.04
F5	26.43 ± 0.25	0.40 ± 0.41	0.48 ± 0.35	16.66 ± 0.37	1.2 ± 0.06
F6	29.32 ± 0.18	0.47 ± 0.53	0.55 ± 0.43	14.54 ± 0.25	1.17 ± 0.03
F7	29.34 ± 0.43	0.40 ± 0.36	0.49 ± 0.22	18.36 ± 0.34	1.22 ± 0.05
F8	27.68 ± 0.51	0.41 ± 0.43	0.48 ± 0.43	14.5 ± 0.43	1.17 ± 0.04
F9	27.86 ± 0.35	0.38 ± 0.33	0.46 ± 0.52	17.39 ± 0.18	1.21 ± 0.08

Table 3: *In vitro* quality control parameters for tablets

Formulations	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)
F1	302.5±0.07	4.1±0.06	0.58±0.05	3.8±0.05	95.67±0.06	4.5±0.05
F2	300.4±0.05	4.0±0.05	0.61±0.08	3.9±0.05	98.54±0.07	5.1±0.07
F3	299.6±0.12	4.1±0.08	0.56±0.07	4.5±0.07	101.43±0.05	5.9±0.09
F4	311.6±0.07	4.3±0.11	0.59±0.09	4.0±0.06	100.78±0.07	5.6±0.07
F5	307.4±0.11	4.5±0.07	0.64±0.11	4.2±0.07	96.41±005	4.9±0.03
F6	300.7±0.05	4.1±0.12	0.50±0.12	3.5±0.02	98.65±0.04	5.4±0.07
F7	301.3±0.07	4.4±0.07	0.63±0.11	4.0±0.07	108.24±0.07	5.2±0.05
F8	296.2±0.09	4.0±0.05	0.50±0.05	3.7±0.05	102.56±0.05	4.6±0.05
F9	297.3±0.05	4.2±0.09	0.55±0.07	4.2±0.10	99.21±0.07	5.4±0.04

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Table 4: Dissolution Data of Nifedipine Tablets

(hr)	CUMULATIVE PERCENTAGE DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	23.57	14.09	10.98	45.56	26.77	20.45	46.23	15.14	10.77
1	32.12	25.45	18.67	62.54	37.89	29.45	58.42	29.81	23.91
2	42.45	37.28	24.35	80.32	46.24	39.98	65.90	35.34	35.23
3	53.10	44.31	29.34	98.36	55.23	47.99	73.56	40.52	39.13
4	69.66	52.67	36.68		63.25	54.91	79.54	48.53	41.1
5	76.33	66.78	40.31		78.9	65.46	81.56	53.64	47.97
6	84.01	75.32	47.76		89.56	71.47	88.45	59.54.	52.57
7	96.77	81.04	54.72		97.66	77.32	90.67	63.53	59.49
8		90.73	65.33			85.49	97.56	69.46	63.67
9		98.76	69.90			91.12		72.53	67.82
10			77.20			99.55		78.23	70.32
11			86.22					81.56	76.39
12			99.36					88.78	80.21

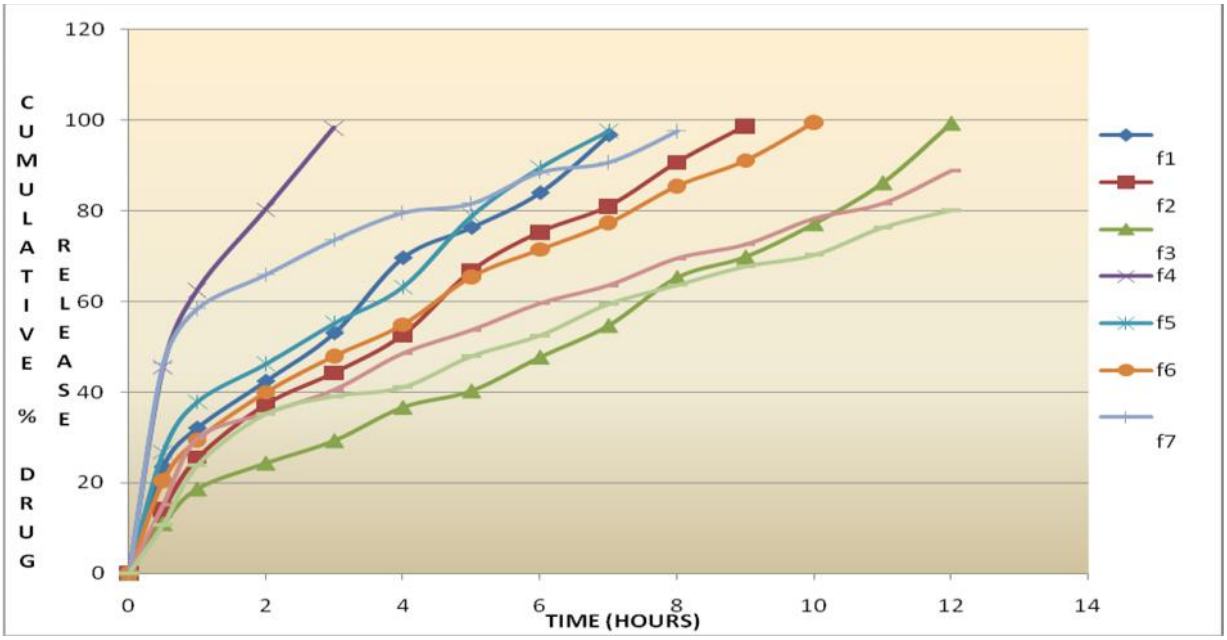

Fig 1: Dissolution profile of nifedipine floating tablet

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Table 5: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
10.98	0.5	0.707	1.041	-0.301	1.949
18.67	1	1.000	1.271	0.000	1.910
24.35	2	1.414	1.386	0.301	1.879
29.34	3	1.732	1.467	0.477	1.849
36.68	4	2.000	1.564	0.602	1.802
40.31	5	2.236	1.605	0.699	1.776
47.76	6	2.449	1.679	0.778	1.718
54.72	7	2.646	1.738	0.845	1.656
65.33	8	2.828	1.815	0.903	1.540
69.9	9	3.000	1.844	0.954	1.479
77.2	10	3.162	1.888	1.000	1.358
86.22	11	3.317	1.936	1.041	1.139
99.36	12	3.464	1.997	1.079	-0.194

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.

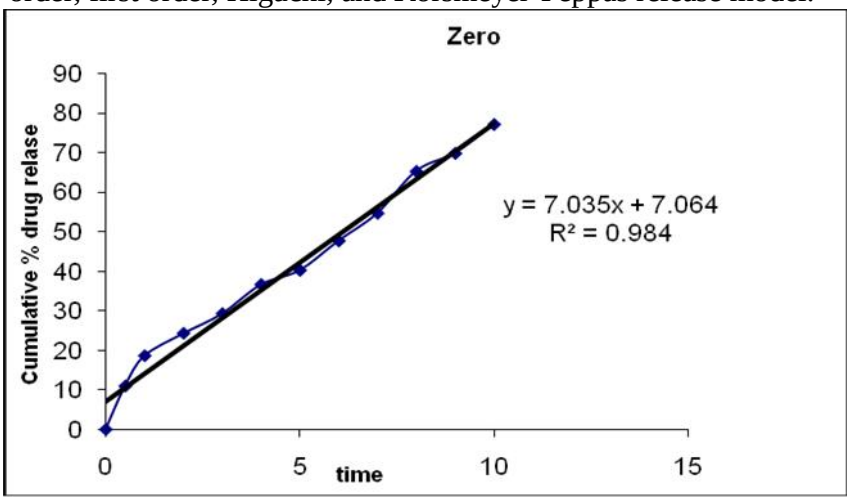

Fig 2 : Zero order release kinetics graph

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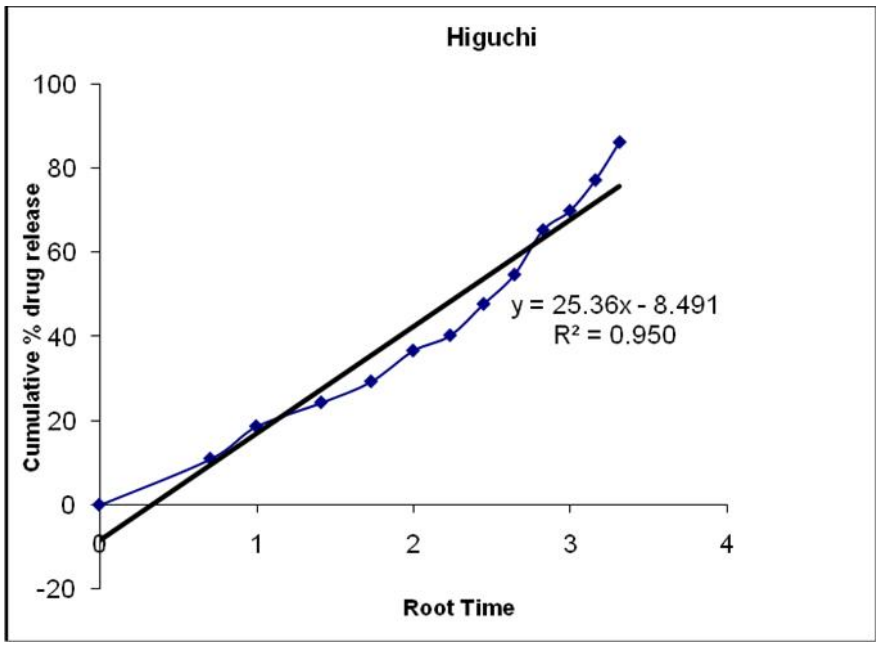

Fig 3 : Higuchi release kinetics graph

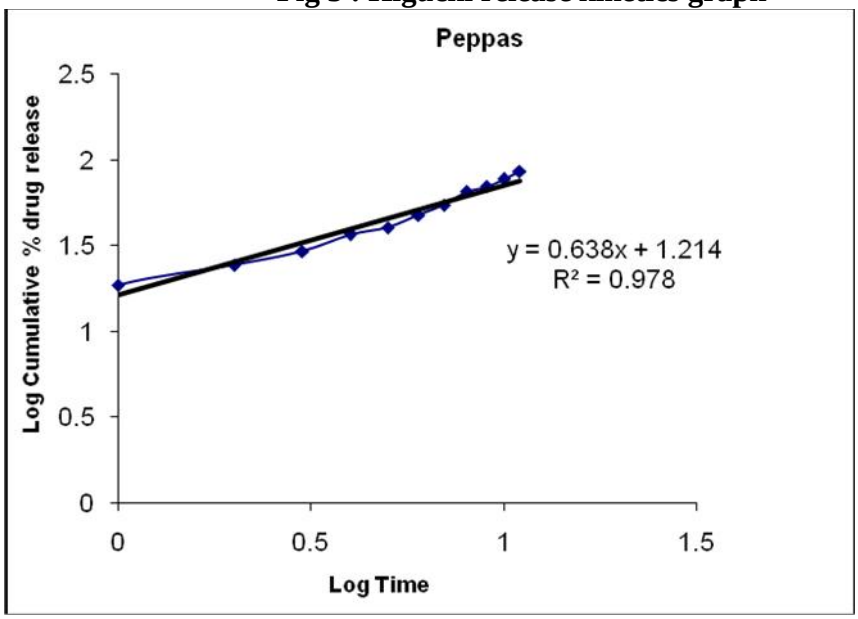

Fig 4: Kars mayer peppas graph

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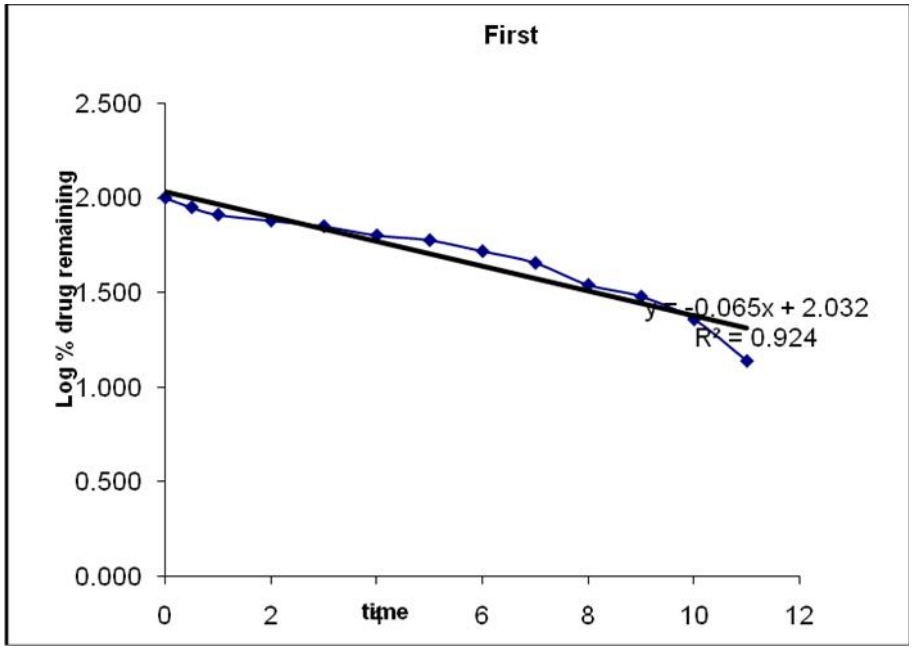

Fig 5: First order release kinetics graph

From the above graphs (Fig 2, 3, 4&5) it was evident that the formulation F3 was followed Zero order release mechanism.

CONCLUSION

An oral sustained released dosage form offer many advantages for drugs having absorption from the upper gastrointestinal tract and improves the bioavailability of medications that are characterized by the narrow absorption window. A Gastro retentive released floating matrix tablets was developed with polymers like Gum cyamposis, Xanthan gum and sodium alginate & effervescent substance sodium bicarbonate with floating and swellable properties, Where the polymers act as a release retarding agent and the effervescent mixture aid for floatation. The optimized formulation followed zero order kinetics. Hence the formulated systems F3 have better bioavailability of drug due to increase gastric residence time. Because floating tablets remains float in stomach reason due to this absorption of window increases and hence the bioavailability of formulation code F3 increased.

ACKNOWLEDGMENT

The authors are thankful to SURA Laboratories, Hyderabad for providing gift samples.

REFERENCE

1. Leon, Lachman., & Herbert A. Liberman. *The Theory and Practice of Industrial Pharmacy.* 3rd Edition. CBS, New Delhi, 2009, 132-34.
2. Robinson, J. R., Lee, V.H.L. *Controlled Drug Delivery: Fundamentals and Applications*. 2nd edition, Marcel Dekker, New York, 1978: 256-68.
3. Ross and Wilson. *Anatomy Physiology and Health Education.* 9th edition, Churchill Livingston, London, 2005, 168-79.
4. Brahmankar, D. M., Jaiswal, S. B. *Biopharmaceutics and Pharmacokinetics: A Treatise.* 1st edition, Vallabh Prakashan, New Delhi, 1995, 223-34.
5. Gennaro, R. A., Remington. *The science and practice of pharmacy*. 20th edition, Lippincott Williams, New York, 2000, 312-45.
6. Ancel HC, Allen LV, Popovich NG. Pharmaceutical dosage forms and drug delivery systems. 5th edition,

New Delhi, Lippincott Williams & Wilkins, 2005, 311-12.
7. Banker, G. S., Rhodes, C. T. *Modern pharmaceutics*. 3rd edition, Marcel Dekker: New York, 1996,423-56.
8. Desai, S., & Olton, S. A Floating Controlled Release System: In-Vitro and In-Vivo Evaluation. *J. Pharm. Res*., 1993: 10, 1321-1325.
9. Shweta, Arora. Floating Drug Delivery: A Review. *aaps pharmscitech.*, 2005: 47(11), 268-272.
10. Chein, Y. W. *Novel Drug Delivery Systems.* 2nd edition, Marcel Dekker, New York, 1992, 434-56.
11. Vyas, S. P., Khar, R, K. *Controlled drug delivery: concepts and advances.* 1st edition, Vallabh Prakashan, New Delhi, 2002, 345-56.

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