International Journal of Innovative Pharmaceutical Sciences and Research
www.ijipsr.com

FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF FLOATING MATRIX TABLET OF REPAGLINIDE

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Abstract

The purpose of the study was to prolong the gastric residence time of Repaglinide by designing its floating tablets and to study the influence of natural polymers like Xanthum gum, Guar gum, Boswellia Ovalifoliolata, Anogeissus Pendula on its release rate. Sodium bicarbonate was added as a gas generating agent, produced carbon dioxide in the gastric acidic environment which helped in maintain the buoyancy. The floating matrix controlled release tablets of Repaglinide were prepared by direct compression method. The prepared tablets were evaluated for physical properties, content uniformity, hardness, friability, floating lag time and *In vitro* drug release. The hardness of all formulations was found to be in the range of 4.0-5.0 kg/cm2. Among all these formulations F3 was the optimized best formulation which has shown better buoyancy time 79sec and drug release 90.67% in 5hrs.

Key words: Floating matrix tablets of Repaglinide, Xanthum gum, guar gum, Boswellia Ovalifoliolata, Anogeissus Pendula.

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INTRODUCTION

Diabetes Mellitus

The number of patients with diabetes mellitus is predicted to increase dramatically worldwide With in the coming decades because of continued population growth, aging, urbanization, and the increasing prevalence of obesity and a sedentary lifestyle. Diabetes mellitus will thus be one of the most prominent threats to human health in the 21st century. Predicted estimates of the prevalence of patients with diabetes mellitus within the coming decades range up to more than 300 million, predominantly those with type 2 diabetes mellitus.[1]

Anti-Diabetic Drugs

Anti-diabetic drugs are medicines developed to stabilize and control blood glucose levels among people with diabetes. Anti-diabetic drugs are commonly used to manage diabetes.

Anti-diabetic drugs are used for the management of diabetes. Six types of anti-diabetic drugs are approved for the treatment of diabetes mellitus: sulfonylureas, biguanides, alpha-glucosidase inhibitors, glitazones, meglitinides, and insulin. Primary treatment goals for patients with diabetes mellitus include achievement of blood glucose levels that are as close to normal as possible to prevent diabetic complications. Both non-pharmacologic and pharmacologic therapies are used for achieving glycaemic control among patients with diabetes mellitus. Non-pharmacologic approaches include a healthy diet, exercise, and weight loss and are generally the first steps in treating type 2 diabetes mellitus. Later, patients will require drugs that stimulate β-cells to make more insulin and/or drugs that help insulin work better.[3]

Anti-diabetic drugs are not designed to cure diabetes, but they help diabetes patients to keep their condition under control and lower the risk of diabetes complications. People with diabetes may need to take anti-diabetic drugs for their whole lives in order to control their blood glucose levels and avoid hypoglycemia and hyperglycemia.[1]

FLOATING DRUG DELIVERY SYSTEM [2,3,4,5]

The concept of FDDS was first described in the literature as early as 1968, when Davis (1968) disclosed a method to overcome the difficulty experienced by some persons of gagging or choking after swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing pill having a density of less than 1.0g/cm^3, so that pill will float on water

surface. Since then several approaches have been used to develop an ideal floating drug delivery system.[4]

The gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms that reside in the stomach for a longer period of time than conventional dosage forms. There are many difficulties faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized. Gastro-retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.[2]

MATERIAL & METHOD:

MATERIAL:

Repaglinide obtained as gift sample from Aurobindo Pharma Ltd. Hyderabad, **Boswellia ovalifoliolata, Anogeissus pendula,** purchased from SV University, Tirupati, **Xanthum gum**, **Guar gum**, **Sodium bicarbonate**, **Citric acid, Micro crystalline cellulose, Talc, Magnesium stearate** are purchased from Sd Fine –Chem Pvt, Mumbai.

METHOD:

Preparation of floating matrix tablets of Repaglinide: Floating matrix tablets of Repaglinide were prepared by Direct Compression method.[Table no.6]

Procedure: First Accurately weighed quantity of Repaglinide with each polymer i.e. Boswellia Ovalifoliolata, Anogeissus Pendula, Xanthum gum and Guar gum are mixed with Microcrystalline cellulose in different ratios in different mortars given in table no.6. Sufficient quantity of distilled water and pass through a # 22 mesh sieve. Then granules were dried at 40 ^{o}C and dried .Granules were lubricated with Talc and Magnesium stearate and compressed into tablets on a 10-station rotator punching machine using 4mm concave punches. Each Tablet contains 100mg of Repaglinide.

Table no. 1: Composition of floating matrix tablet of repaglinide

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Repaglinide	2	2	2	2	2	2	2	2	2	2	2	2
Boswellia ovalifoliolata	2	4	6	-	-	-	-	-	-	-	-	-
Anogeissus pendula	-	-	-	2	4	6	-	-	-	-	-	-
Xanthum gum	-	-	-	-	-	-	2	4	6	-	-	-
Guar gum	-	-	-	-	-	-	-	-	-	2	4	6
Sodium bicarbonate	30	25	20	30	25	20	30	25	20	30	25	20
Citric acid	5	5	5	5	5	5	5	5	5	5	5	5
Micro crystalline cellulose	60	63	66	60	63	66	60	63	66	60	63	66
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total (mg)	100	100	100	100	100	100	100	100	100	100	100	100

RESULTS AND DISCUSSION

Floating matrix tablet of repaglinide were prepared and evaluated. In the present study 12 formulations with variable concentration of polymer were prepared and evaluated for physio-chemical parameters, in vitro release studies and release Kinetics.

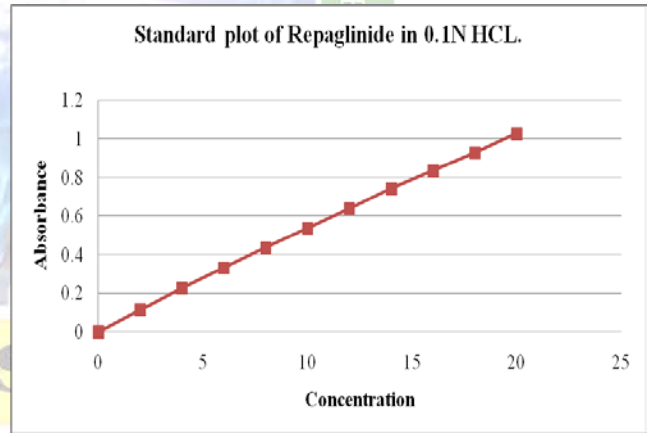
Standard plot of Repaglinide in 0.1N HCL

An accurately weighed quantity of Repaglinide (100)mg was dissolved in 10 ml of methanol and made up to 100ml with 0.1N Hcl to generate a primary stock solution having a concentration of 1mg/ml. Five ml of the primary stock solution was further diluted to 100ml to produce a secondary stock solution having a a concentration of 50µg/ml.1-5ml aliquots of the secondary stock solution were further diluted to 10m to produce std solutions having a concentrations of 5-25µg/ml. The absorbance of the solutions measured at 243.5nm using doble beam UV spectrophotometer against 0.1N HCl as a blank. The plot of absorbance vs concentration of (µg/ml) was plotted and data was subjected to linear regression analysis in Microsoft Excel.

Table 2: Calibration of Repaglinide in 0.1 N HCL

Concentration µg/ml	Absorbance
2	0.114
4	0.227
6	0.332
8	0.438
10	0.539
12	0.64
14	0.744
16	0.835
18	0.93
20	1.029

Fig 1: STD Plot of Repaglinide Drug



DRUG POLYMER INTERACTION STUDY (FTIR)

Infrared spectrophotometry is a useful analytical technique utilized to check the chemical interaction between the drug and other excipients used in the formulation. One mg of sample was powdered and intimately mixed with 10mg of dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler and the spectrum was recorded by scanning in the wavelength region of 400-400$_{cm}^{-1}$ in an FTIR spectrophotometer (Jasco 460 plus, japan).The

IR spectrum of the drug was compared with that of the physical mixture to check for any possible drug-excipients interaction.

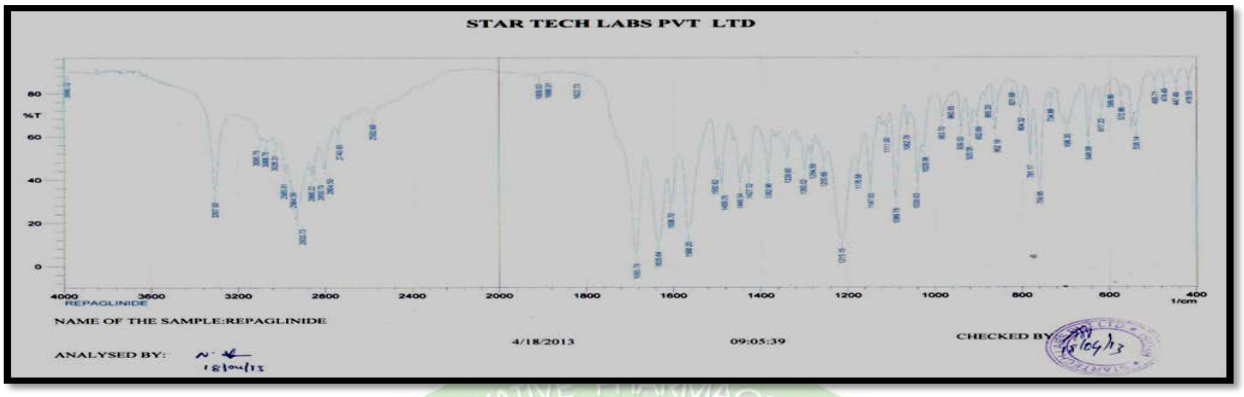


Fig 2: FTIR of Repaglinide Drug

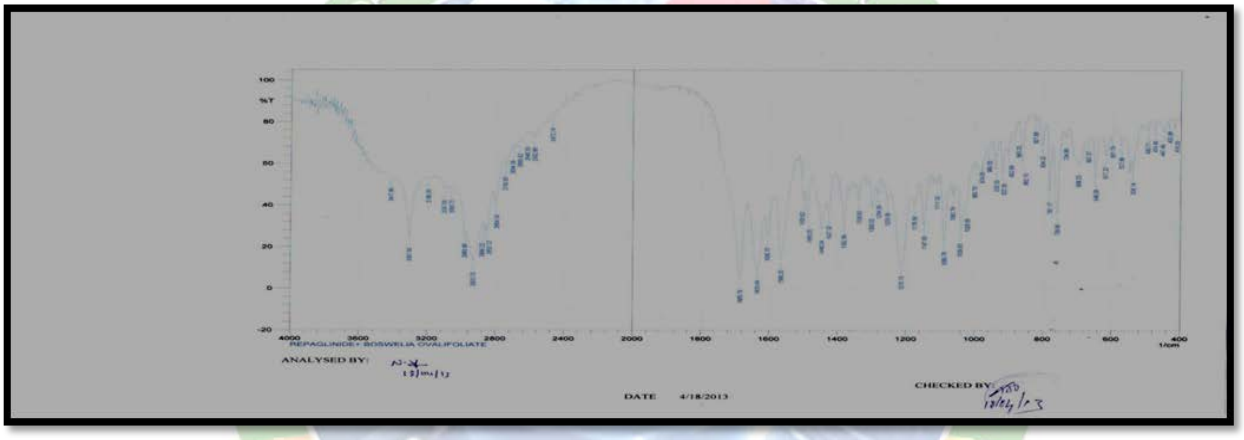


Fig 3: FTIR of Repaglinide Drug and Boswellia ovalifoliolata gum

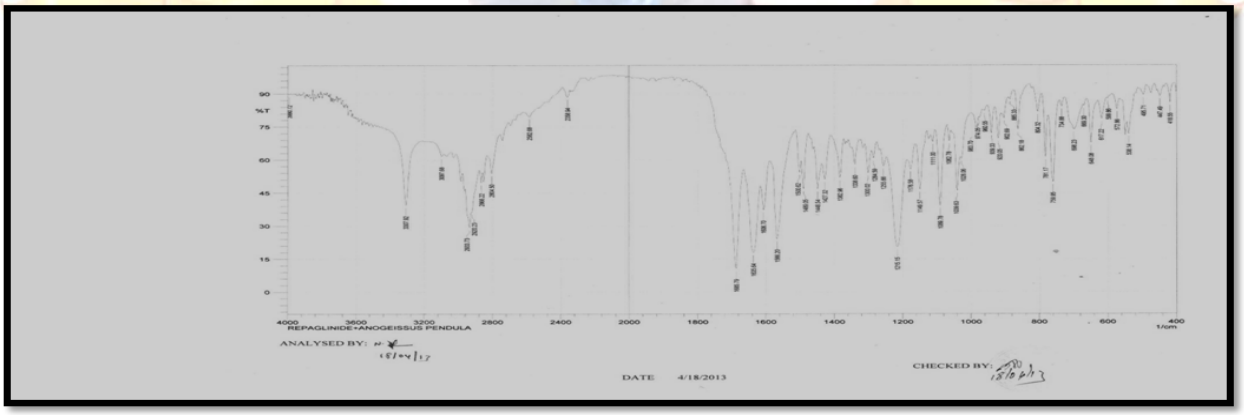


Fig 4: FTIR of Repaglinide Drug and Anogeissus pendula gum

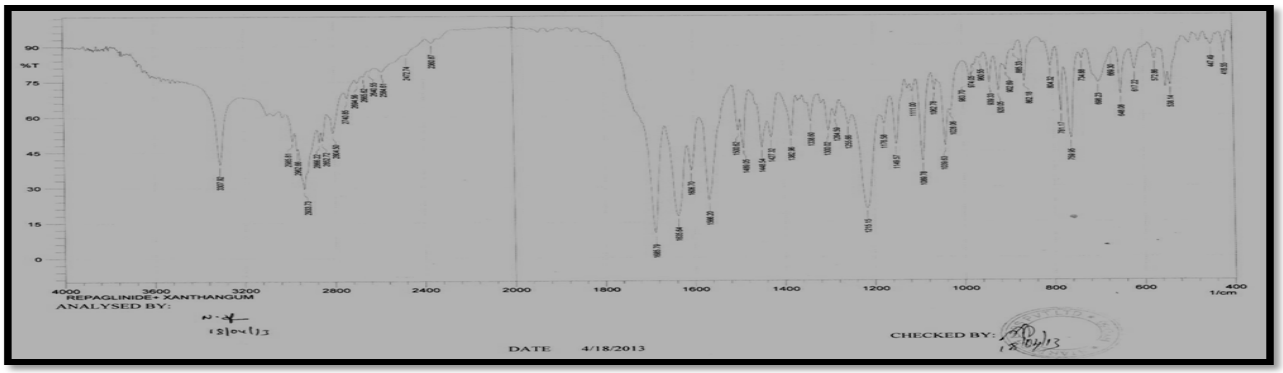


Fig 5: FTIR of Repaglinide Drug and Xanthum gum

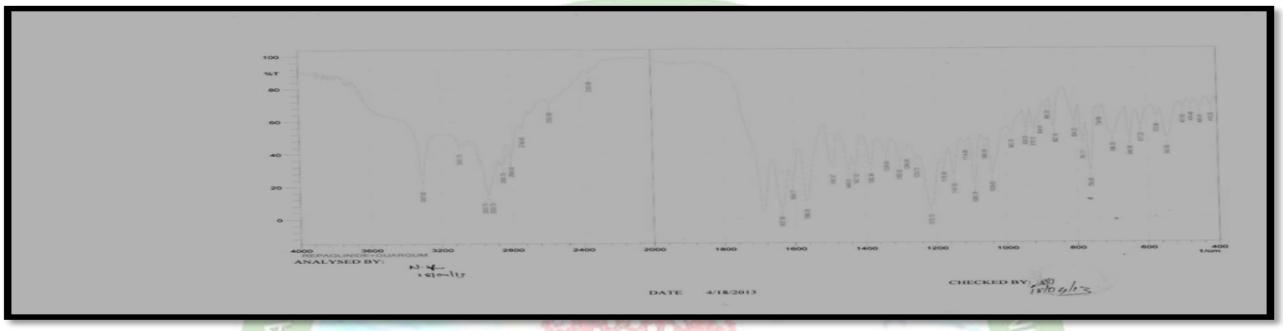


Fig 6: FTIR of Repaglinide Drug and Guar gum.

Pre-Formulation Parameters [6, 7, 8]

Precompression parameters such as angle of repose, Compressibility index and Hausner ratio which are evaluated for prepared tablets are given in following table:

Table 3: Preformulation Studies of All Formulation

Formulations	Angle of repose (θ)	Compressibility Index (%)	Hausner's ratio
F_1	32.21	14.63	1.171
F_2	32.61	15.55	1.184
F_3	32.21	18	1.219
F_4	29.24	18	1.219
F_5	32.61	19	1.242
F_6	30.96	11	1.125
F_7	23.26	18	1.22
F_8	24.70	15.55	1.18
F_9	21.30	18	1.22
F_{10}	27.47	19	1.25
F_{11}	27.92	16	1.22
F_{12}	28.36	19	1.24

Evaluation of tablet: [9, 10]

Weight variation:

Evaluation Twenty tablets were randomly selected from each batch individually weigh, the average weight and standard deviation of 20 tablet calculated (Krishanaiah et al., 2003). Table no-6

Thickness:

The thickness of the tablet was measured by using digital venire caliper, twenty tablets from each batch were randomly selected and thickness was measured (The British Pharmacopoeia, 2005).

Hardness:

Hardness was measured using Pfizer hardness tester, for each batch three tablets were tested (The United State of Pharmacopoeia, 1995). (Table no-6)

Friability:

Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After revolution the tablets were dusted and weighed. (Chaudhari PD, 2005).

Table 4: Evaluation of tablet of All Formulation

Formulations	Thickness (mm)	Weight Variation (%)	Hardness (kg/cm^2)	Friability (%)
F1	3.56	0.25	5.1	0.75
F2	3.51	0.24	4.2	0.77
F3	3.47	0.26	4.4	0.79
F4	3.22	0.38	4.1	0.85
F5	3.41	0.47	4.5	0.82
F6	3.03	0.31	4.3	0.86
F7	3.44	0.37	4.2	0.89
F8	3.19	0.51	4.4	0.84
F9	3.12	0.42	4.5	0.87
F10	3.14	0.55	4.2	0.89
F11	3.45	0.62	4.4	0.98
F12	3.34	0.61	4.1	0.95

Buoyancy study: The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100-ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Table 5: Buoyancy study of All Formulation

Batch No	Buoyancy lag time (sec)	Floating duration (hrs)
F1	75	5
F2	70	5
F3	79	5
F4	71	5
F5	68	5
F6	65	5
F7	63	5
F8	66	5
F9	67	5
F10	71	5
F11	72	5
F12	68	5

The Buoyancy study was performed for all the 12 formulations and Results are shown in Table above. The time of Buoyancy of the Matrix floating tablet were found to be between 63 secs to 79 secs.

At initial time **After 50 seconds** **After 70 seconds**

Fig 7: *In vitro* buoyancy studies of floating matrix tablets of Repaglinide.

***In vitro* Drug Release Study:**

In vitro drug release study was performed using t5ype-II (paddle) apparatus at 50 rpm in 900 ml simulated gastric fluid of 1.2 pH(0.1N HCl) for 5 hrs. Temperature was maintained at 37 ± 0.5oC. The 5 ml sample was withdrawn at predetermined time intervals and replaced with same fresh dissolution media. The withdrawn samples were filtered through membrane filter 0.45µm and analyzed by using UV spectrophotometer at λmax 243.5 nm for 12 hrs. This test was performed on 3 tablets and mean ± SD was calculated.

Table 6: Cumulative % Drug release of (F1-F3)

Time (Mins)	Cumulative % drug release (F1)	Cumulative % drug release (F2)	Cumulative % drug release (F3)
30	14.63	13.91	13.11
60	20.39	19.68	19.12
120	34.51	32.64	31.31
180	49.06	48.63	46.36
240	79.15	75.63	74.38
300	91.17	91.04	90.67

Fig 8: Dissolution profile of F1 to F3.

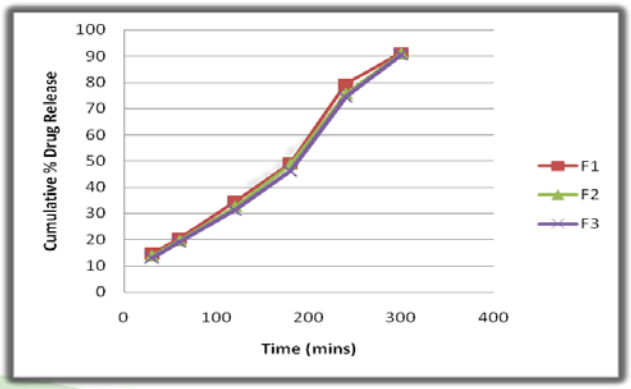


Table 7: cumulative % drug release of (F4-F6)

TIME (Mins)	Cumulative % drug release (F4)	Cumulative % drug release (F5)	Cumulative % drug release (F6)
30	16.96	16.31	16.17
60	23.15	22.67	22.17
120	37.22	36.69	36.14
180	52.65	52.16	51.57
240	82.41	82.13	81.88
300	92.86	92.41	92.10

Fig 9: Dissolution profile of F4 to F6.

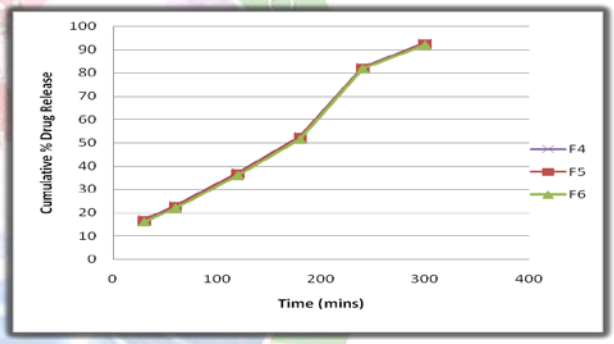


Table 8: cumulative % drug release of (F7-F9)

TIME (Mins)	Cumulative % drug release (F7)	Cumulative % drug release (F8)	Cumulative % drug release (F9)
30	18.91	18.18	17.16
60	25.38	24.64	24.17
120	41.23	41.11	39.84
180	64.71	64.22	63.81
240	89.55	89.21	88.64
300	97.98	97.27	96.63

Fig 10: Dissolution profile of F7 to F9.

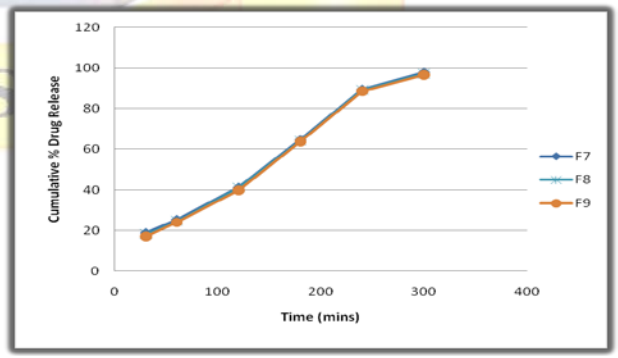
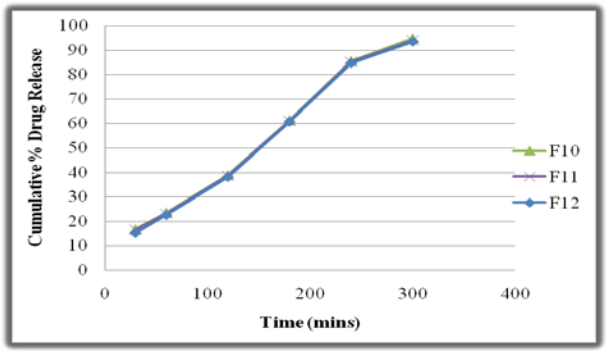


Table 9: cumulative % drug release of (F10-F12)

TIME (Mins)	Cumulative % drug release (F10)	Cumulative % drug release (F11)	Cumulative % drug release (F12)
30	16.81	16.53	15.21
60	23.57	23.11	22.59
120	38.91	38.61	38.15
180	61.25	61.11	60.77
240	85.45	85.13	84.67
300	94.67	94.03	93.49

Fig 11: Dissolution profile of F10 to F12



KINETICS RELEASE OF BEST FORMULATION (F3)

Table No.10: Kinetics Release of Best Formulation F3

TIME (mins)	ABSORBANCE	CONC Mg/ml	CUMULATIVE % DRUG RELEASE	% DRUG RETAINED	LOG % DRUG RETAINED	LOG TIME	LOG % DRUG RELEASE
30	0.006	0.376	16.96	83.04	1.919	1.477	1.229
60	0.017	0.514	23.15	76.85	1.885	1.778	1.364
120	0.020	0.827	37.22	62.78	1.797	2.079	1.570
180	0.024	1.17	52.65	47.35	1.675	2.255	1.721
240	0.037	1.731	82.41	17.59	1.245	2.380	1.915
300	0.042	1.875	92.86	7.14	0.853	2.477	1.967

Fig. 12: Zero Order

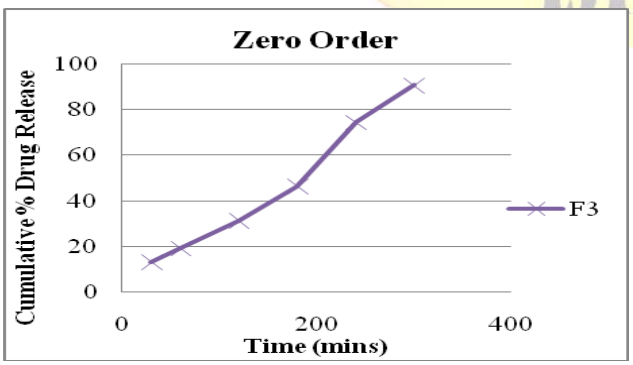


Fig.13: First Order

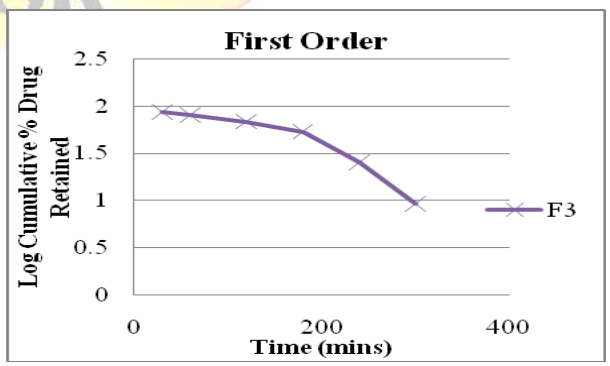


Fig.14: Higuchi

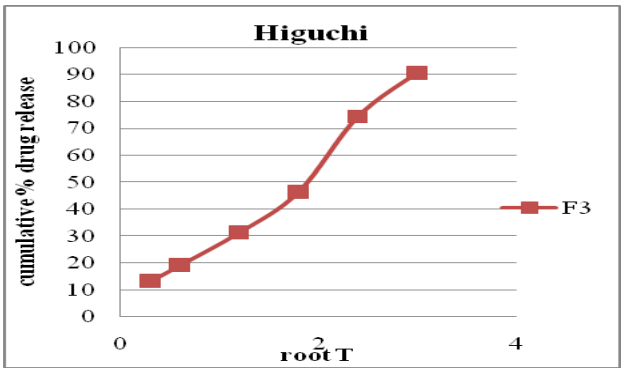
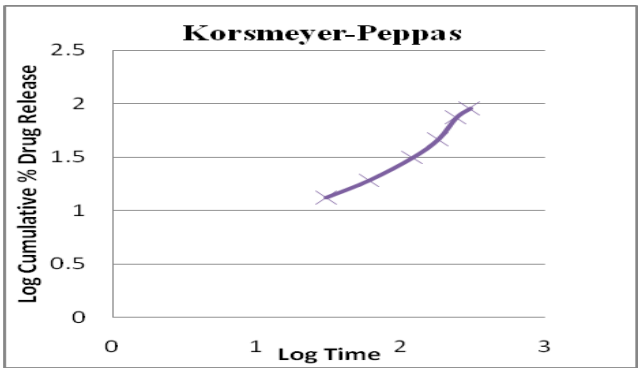


Fig.15: Korsmeyer-Peppas



Stability studies:

The selected formulations was evaluated for short term stability studies which was stored at 40°C at 75% RH tested for 3 months and were analyzed periodically for their physical parameters, Thickness, Hardness, Friability, in vitro drug release time and drug content at 30 days interval. The residual drug contents of formulations were found to be within the permissible limits and the values were shown in the table no.14.

Table 11: Accelerated Stability Testing

Parameters	Before stability studies	After 1 month	After 2 months	After 3 months
Thickness (mm)	3.47	3.47	3.43	3.35
Hardness (kg/cm^2)	4.1	4.1	4.1	4.1
Friability (%)	0.79	0.79	0.84	0.89
Drug content uniformity	99.54	99.54	99.53	99.53
***In vitro* drug release study**	90.67	90.67	90.65	90.62

CONCLUSION

Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, buoyancy, content uniformity, all the formulations were found within the permissible range. Finally it was concluded that: Among all the formulations (F1-F12), it was observed that formulation-3 has shown better buoyancy (79 secs) and dissolution profile. So Formulation-3 was found to be the best formulation among others.

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