FORMULATION AND CHARACTERIZATION OF GASTRORETENTIVE FLOATING TABLETS OF MIGLITOL USING HYDROPHILIC POLYMERS

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ABSTRACT : In the present investigation, formulation of Miglitol floating tablets using various polymers and sodium bicarbonate was used as gas generating agent. Absorption maxima were determined and calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimised. Prepared powder blend was subjected to various physical chemical properties. They were found to be within limits. After compressing the tablets, they were evaluated for post compression studies such as weight variation, thickness, hardness, friability and drug content. From the dissolution data, Among all formulations F6 and F7 formulations shown maximum drug release at 12 hrs i.e. 98.12 %.Based on concentration of polymers F7 was considered as optimised formulation. The optimized formulation dissolution data was subjected to release kinetics. From the release kinetics data it was evident that the formulation followed Kars mayerpeppas mechanism of drug release.

Keywords: Miglitol, Sodium bicorbonate, HPMC K 100M, HPMC 4M, HPMC K15M, Floating tablets.

I. INTRODUCTION

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance, and flexibility in formulation.[1] Gastroretentive 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 wastage, and improves solubility for drugs that are less soluble at a higher pH. Also it has applications for the local drug delivery to the stomach and proximal small intestine. Gastricretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[2]

Miglitol is an oral anti- diabetic drug that acts by inhibiting the ability of the patient to breakdown complex carbohydrates into glucose. It is primarily used in diabetes mellitus type 2 for establishing greater glycemic control by preventing the digestion of carbohydrates (such as disaccharides, oligosaccharides and polysaccharides) into monosaccharide which can be absorbed by the body. The biological half life of miglitol is 2 hours.[3] Oral floating dosage form by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic, or oxidative reactions occurred during processing of dosage forms. [4]
In the present study attempts were made to prepare, optimize and evaluate floating tablets for effective therapeutic efficacy, sustained release of drug with reduced dose frequency and enhanced patient compliance. Hence, an attempt is made in this research work to formulate floating tablets of miglitol using HPMC K15M HPMC K4M and HPMC K100M and sodium bicarbonate.

II. MATERIALS AND METHODS

2.1. Materials

Miglitol was obtained from Arudavis labs private limited (Tamilnadu, India). HPMC Grades were procured from Merck Specialities Pvt Ltd, Mumbai, India and other chemicals and reagents used were of analytical grade.

2.2 Methods

Drug – Excipient compatibility studies[5]

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 bruker IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Formulation development of Tablets:[6]

Miglitol and all other ingredients 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.The tablets were prepared by using direct compression method.

Optimization of Sodium bicarbonate concentration:

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed floating lag time and floating duration were observed. Based on that the concentration of sodium bicarbonate was finalized and preceded for further formulations.

Table-1: Optimisation Sodium bicarbonate concentration

S.No	Excipient Name	O_1	O_2	O_3
1	Miglitol	25	25	25
2	HPMC K 100M	60	60	60
4	Sodium bicarbonate	20	40	60
5	Mg.Stearate	4	4	4
6	Talc	4	4	4
8	MCC pH 102	Q.S	Q.S	Q.S
	Total weight	200	200	200

Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimised.

Table-2:Formulation composition for floating tablets

F. No.	Miglitol	Hpmc K 4M	Hpmc K 15M	Hpmc K 100M	$NaHCO_3$	Mg. Stearate	Talc	MCC pH 102	Total tablet weight (mg)
F1	25	20	--	--	60	4	4	QS	200
F2	25	40	--	--	60	4	4	QS	200
F3	25	60		--	60	4	4	QS	200
F4	25	--	20	--	60	4	4	QS	200
F5	25	--	40	--	60	4	4	QS	200
F6	25	--	60	--	60	4	4	QS	200
F7	25	--	--	20	60	4	4	QS	200
F8	25	--	--	40	60	4	4	QS	200
F9	25	--	--	60	60	4	4	QS	200

Evaluation of post compression parameters for prepared Tablets[7,8,9]

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

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

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

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content:

Randomly Select ten tablets of each batch and triturated as fine powder. The powder equivalent to one tablet weight of Miglitol were weighed accurately and 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 0.1N HCL. 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. 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**

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 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml fresh media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 228 nm using UV-spectrophotometer.

Application of Release Rate Kinetics To Dissolution Data:[10]

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.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data ar e fitted to the followingequation.

$$F = K_o\, t$$

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

First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log } (100\text{-}F) = kt$$

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

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

$$F = k\, t1/2$$

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 ofdrug 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.

$$M_t / M_\infty = K\, t^n$$

Where,M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' isthe 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.

3 RESULTS & DISCUSSION

Drug – Excipient compatibility studies

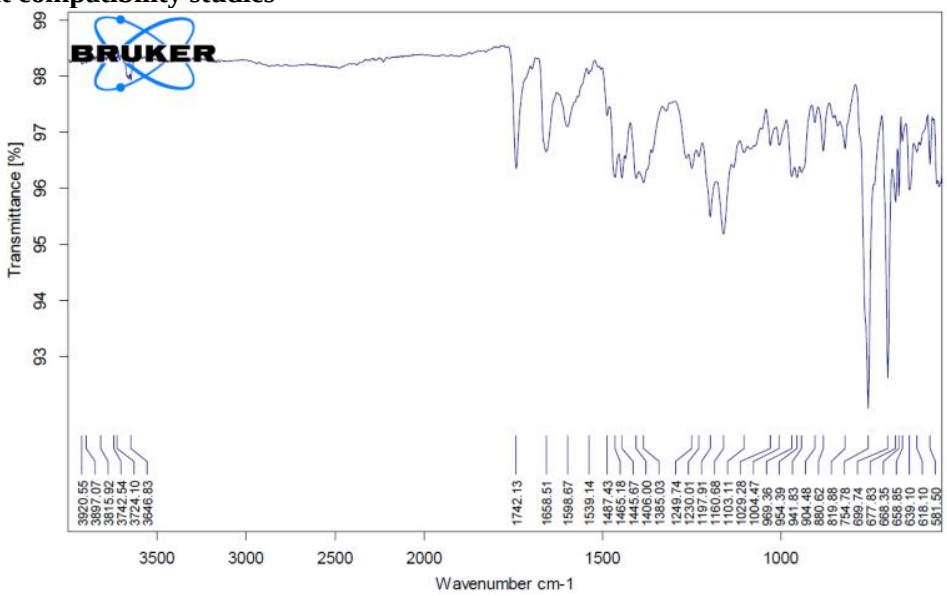

Fig.1. FT-IR Spectrum of Miglitol pure drug.

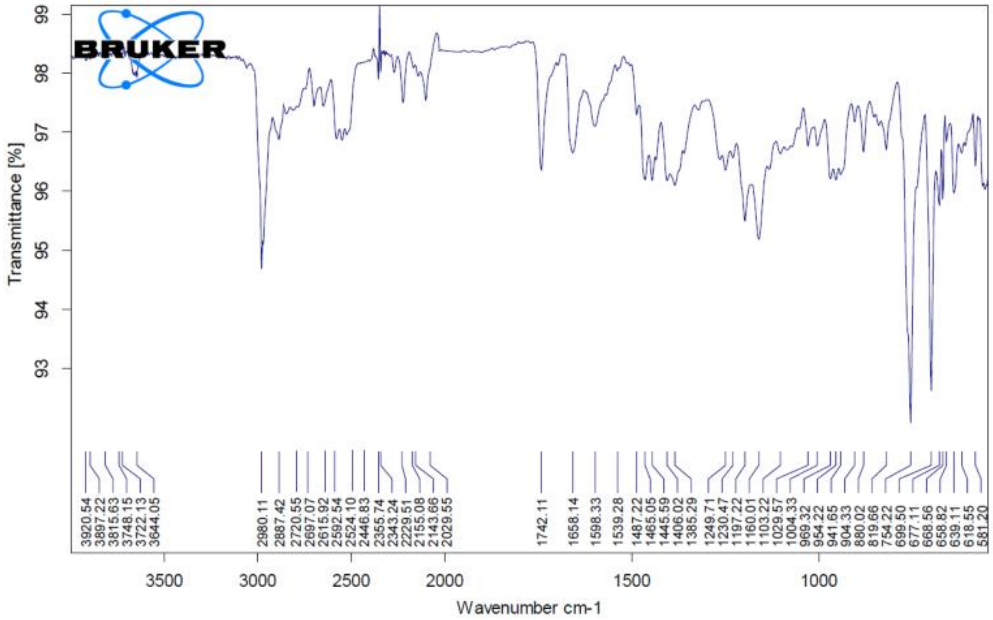

Fig.2.FT-IR Spectrum of Optimised Formulation

The FTIR compatability tests were passed. There was no interaction between drug and excipients. There was no disappearence of characteristic peak of pure drug.

Quality Control Parameters For tablets:

Table-3: In vitro quality control parameters for tablets

F. code	Average Weight (mg)	Hardness(kg/ cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)	Duration of floating time (hr)
F1	102.5±0.1	2.7±0.1	2.13±0.001	0.55±0.1	98.76±0.005	04	3

F2	95.4±0.1	2.6±0.1	2.05±0.15	0.62±0.057	99.45±0.01	03	4
F3	103.6±0.057	3.0±0.1	2.19±0.01	0.63±0.057	98.34±0.005	4.1	6
F4	99.6±0.1	2.8±0.15	2.16±0.015	0.54±0.1	99.87±0.01	4.3	6
F5	96.4±0.58	2.6±0.1	3.0±0.05	0.56±0.057	99.14±0.01	3.1	12
F6	105.7±1.06	2.0±0.11	2.19±0.01	0.58±0.11	97.56±0.01	4.2	12
F7	702.3±0.1	4.1±0.05	0.51±0.05	4.4±0.05	98.42±0.1	3.5	12
F8	695.2±0.05	4.3±0.1	0.49±0.1	4.7±0.1	99.65±0.1	3.6	12
F9	704.3±0.05	5.0±0.05	0.55±0.05	4.6±0.05	99.12±0.1	4.7	12

***In-Vitro* Drug Release Studies**

Table-4: Dissolution Data of Miglitol Tablets Prepared With HPMC K 4 M in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F1	F2	F3
0	0	0	0
0.5	30.73	37.47	12.65
1	62.23	59.93	20.53
2	75.65	65.85	35.89
3	89.45	77.54	45.7
4	92.46	83.45	54.38
5		94.12	61.2
6			79.62
7			94.63
8			
9			
10			
11			
12			

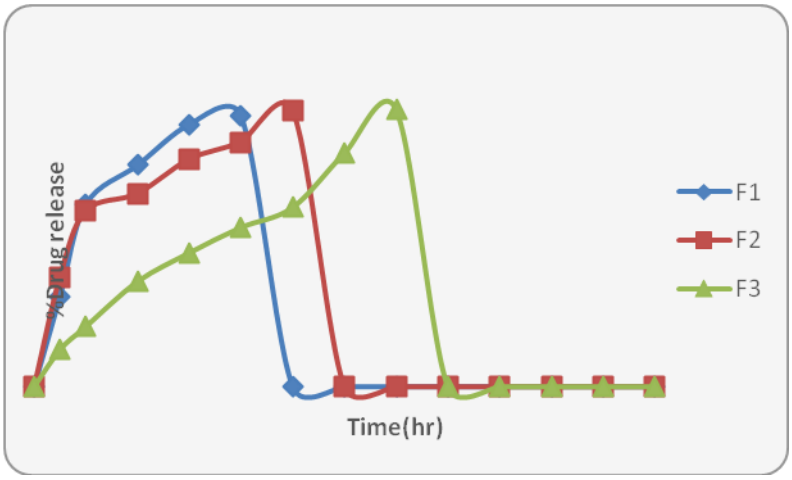

Fig.3. Dissolution profile of Miglitol floating tablets (F1, F2, F3 formulations).

Table-5: Dissolution Data of Miglitol Tablets Prepared with HPMC K 15 M in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F4	F5	F6
0	0	0	0
0.5	24.62	29.02	11.56
1	31.86	35.70	18.56
2	39.35	43.32	20.89
3	47.45	49.25	26.04
4	57.80	55.28	30.43
5	65.25	60.92	45.18
6	70.24	76.08	50.81
7	86.73	80.44	56.89
8	95.34	87.22	64.53
9		90.45	69.43
10			72.83
11			80.45
12			98.12

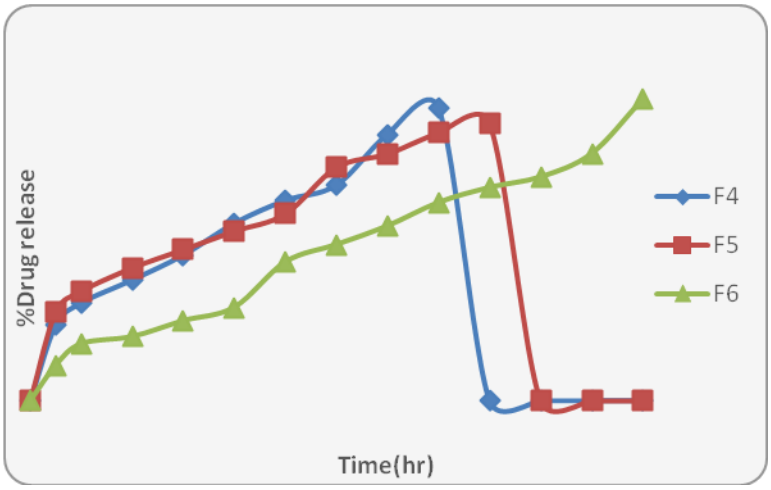

Fig.5. Dissolution profile of Miglitol floating tablets (F4,F5, F6, formulations).

Table-6: Dissolution Data of ketaconazole Tablets Prepared With HPMC K 100 M in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F7	F8	F9
0	0	0	0
0.5	08.12	17.85	06.12
1	17.16	15.12	12.36
2	34.45	20.69	19.56
3	39.15	24.62	20.45
4	43.12	31.86	28.73
5	49.16	39.35	24.62

6	52.16	45.25	30.83
7	65.45	50.24	34.84
8	68.23	56.73	38.34
9	70.12	61.34	47.43
10	79.45	68.52	52.17
11	88.63	75.75	60.41
12	98.12	86.45	79.46

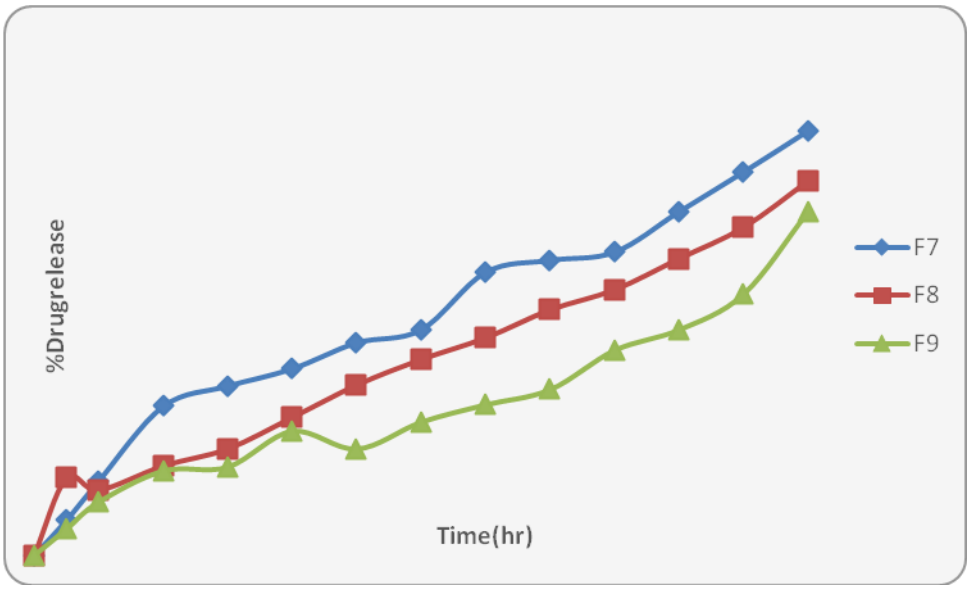

Fig.5. Dissolution profile of Miglitol floating tablets (F7,F8,F9 formulations)

From the dissolution data it was evident that the formulations prepared withHpmc K 14 M and Hpmc K 15 M polymer were retarding the drug release up to12 hours. Formulations prepared with Hpmc K 4 M was unable to retard up to 12 hours. Among all formulations F6 and F7 formulations shown maximum drug release at 12 hrs i.e. 98.12 %.Based on concentration of polymers F7 was considerd as optimised formulation

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.

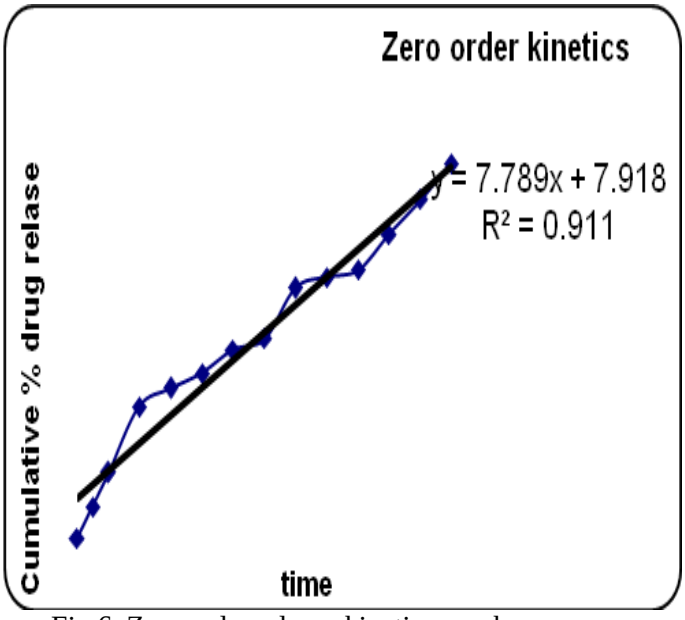

Fig.6. Zero order release kinetics graph

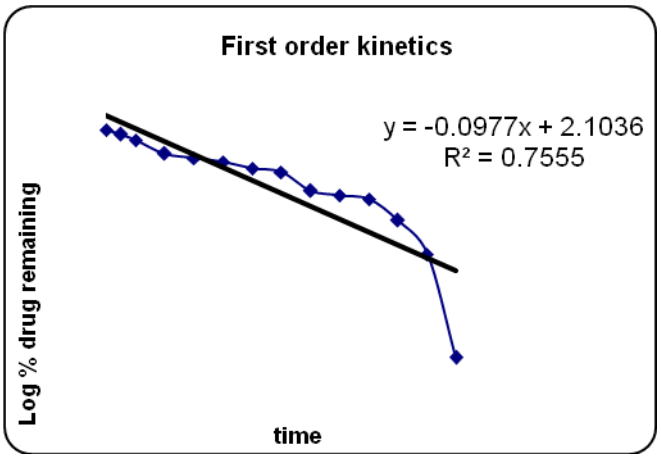

Fig.7. First order release kinetics graph

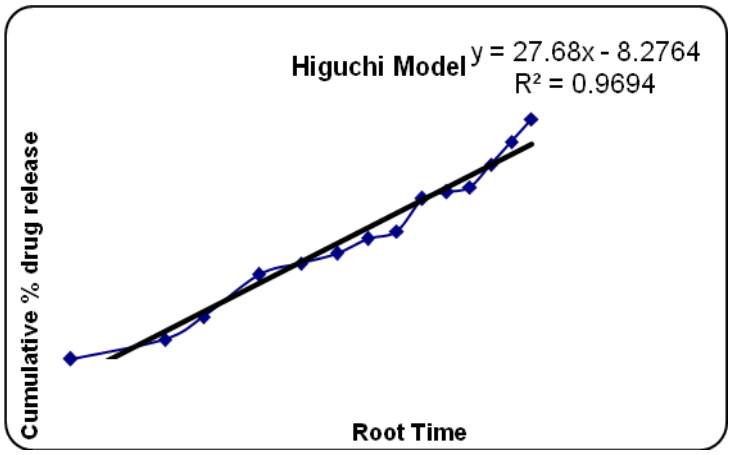

Fig.8. Higuchi release kinetics graph

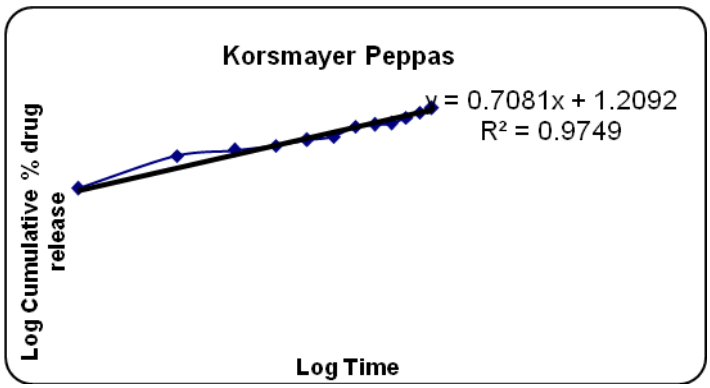

Fig.9. Korsmayer peppas graph

From the above graphs it was evident that the formulation F6 was followed Korsmayer peppas mechanism.

IV. CONCLUSION

The present research work controlled release floating matrix formulation of Miglitol by using various polymers. Absorption maxima were determined and calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimised. Then the formulation was developed by using different concentrations of polymers. The formulation blend was subjected to physical chemical studies and all the formulations were found to be within limits which indicating that the powder blend has good flow properties. Among all formulations F6 and F7 formulations shown maximum drug release at 12 hrs i.e. 98.12 %.Based on concentration of polymers F7 was considerd as optimised formulation. The optimised formulation dissolution data was subjected to release kinetics. From the release kinetics data it was evident that the formulation followedKrossmayerpeppasmechanism of drug release.

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