FORMULATIONANDEVALUATIONOF SUSTAINED RELEASE TABLET OF MIGLITOL

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Abstract: Miglitol has a short biological half-life of 2hrs with poor bioavailability which necessitates multiple daily dosing hence the present study was aimed to develop a sustained release formulation of Miglitol to reduce the dose releated side effects and the dosage regimen. Polymers like ethyl cellulose, guar gum and Carbopol were used for controlling the drug release, and the polymers are mixed in a predetermined ratio. A total12 formulations were prepared and evaluated for pre compression and post compresion parameters, and all the results were found to be within the limits. From the drug and excipients compatability studies(FT-IR) it was confirmed that the drug and excipients have no interactions. The invitro dissolution data for best formulation F12 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation controls the drug release upto 12hours was studied and the optimized formulation F12 shows R^2 value 0.972. As its value nearer to the '1' it is conformed as it follows the First order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport. Hencethe F12 formulation containing Guar gum was considered to be suitable for the formulation of Miglitol controlled release tablets.

Keywords: Miglitol, ethyl cellulose, Guar gum, Carbopol, FT-IR.

1) **Introduction:** Many conventional oral drug dosage forms like tablets and capsules, are formulated to release the active drug moiety immediately after oral administration to obtain rapid and complete systemic drug absorption [1]. Sustained drug release systems can achieve this at predictable and reproducible release rates, have extended duration of action for drugs with short half - life , lowered adverse effets and reduced dose requirement, optimized therapy and better patient compliance [2].

Diabetes mellitus is a chronic metabolic disorder with persistent hyerglycemia due to either absolute insulin deficiency and or insulin resistance. If the body cells do not absorb the glucose, the glucose accumulates in the blood, leading to diabetic neuropathy,nephropathy

and retinopathy. [3]. Miglitol is an oral alpha-glucosidase inhibitor for use in the management of non-insulin-dependent diabetes mellitus (NIDDM) to reduce post prandial hyperglycemia. The biological half-life of miglitol is 2 hrs. The elimination half - life of miglitol from plasma is approximately 2 hours. Miglitol is used along with a proper diet and exercise program to control high blood sugar in people with type 2 diabetes [4]. The objective of the present work is to develop a sustained release tablets for the drug miglitol by direct compression methodusingvariouspolymerssuchas Ethyl cellulose, Carbopol 934P and Guar gum to minimize side effect as well as to improve patient compliance and preventing the fluctuation of the therapeutic concentration of the drug in the body altogether for the better management of the disease.(5)The plan work was drawn with respect to selection of drug candidate, excipients and appropriate biocompatible polymers through preformulation studies including development to suitable analytical methods, develop suitable no. analytical method for the estimation of the drug, evaluate the powder mix for precompression characteristic and tableting characteristics, drug interaction studies by FTIR, compress the formulation according to compatibility study ,evaluate post compression parameters like density,hardness,friability and content uniformityetc. followed by optimizationofformulationparametersanddrug-carriersystemusing appropriate methods,study ofdissolution,Percentageofdrugcontent etc.

2) **Materialsand Methods: Materials:** **Miglitol** obtained from B.M.R ChemicalsHyderabad, Carbopol 934P, Ethyl cellulose were procured from Strides arcolab, Bangalore., Guar gum from Himedia laboratory. Mumbai, Talc, PVP K 30, Magnesium Stearate, Micro Crystalline cellulose from Loba chemie Pvt.Ltd, Mumbai and all other ingredients used were of analytical grade. UV-Vis Spectrophotometer, FTIR 1700S Spectrophotometer(Shimadzu,Japan.), Dissolution test apparatus TDT-08T Dissolution Tester (USP)(LAB India DS-8000), Friabilator USP EF-2,(Eleectrolab, Mumbai) Tablet punching machine (Rimek mini press-1)(10 stations 9.25 mm concavepunches)(Karnavati Engineering Ltd, Mehsana, Gujarat.)

2.1) Preformulation studies:(6)

a) **Solubility**: Solubility of Miglitol was determined in pH 1.2, pH 7.4, and pH 6.8 phosphate buffers by taking excess amount of Miglitol in the solvents, shaken for 24hrs at regular intervals, filtered by using whattmann's filter paper grade no.41 and areanalyzed by spectrophotometrically.

b) **Compatibility Studies** of the pure drug and its formulations along with excipients were subjected to FTIR studies and the potassium bromidedisc (pellet) method was employed.(7)

c) **Identification of Miglitol by determination of UV spectrum of Miglitol:**10mg of Miglitol was dissolved in 10ml of buffers so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution by serial dilution ,a concentration of 100µg/ml and from this concentration of 10µg/ml concentration was prepared and scanned under UV Spectroscopy in the range of 200-400nm.A standard calibration curve for Miglitol at pH 1.2 and pH 6.8 was drawn with absorbance values were plotted against concentration (µg/ml)(8)

2.2) Preparation of miglitol controlled release matrix tablets:[9-13]: Controlled release tablets of Miglitol were prepared by direct compression method using variable concentrations of different polymers like Carbopol 934P, Ethyl cellulose and Guar gum. Direct compression method is widely employed method for production of compressed tablets.

Table 1: Tablet composition of different formulations of Miglitol matrix tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Miglitol	25	25	25	25	25	25	25	25	25	25	25	25
Ethyl cellulose	10	20	30	40	--	--	--	--	--	--	--	--
Carbopol	--	--	--	--	10	20	30	40	--	--	--	--
Guar gum	--	--	--	--	--	--	--	--	10	20	30	40
MCC	100	90	80	70	100	90	80	70	100	90	80	70
PVP K30	10	10	10	10	10	10	10	10	10	10	10	10
Mg.st	2	2	2	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total	150	150	150	150	150	150	150	150	150	150	150	150

Direct compression: In this process the tablets are compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in to the die cavity and forms a firm compact.The drug and the other excipients were passed through 40# sieve together and blended for 10 minutes.The magnesium stearate was passed through 60# sieve and added to the blend of step2 and blended for 5 minutes and compressed the blend of into tablets by using 8mmround punches.[14]

2.3 EvaluationParameters [15-17]

2.3.1.Pre-Compression Parameters:

A. Bulkdensity (D_b)

Bulk density is the ratio of powder to bulk volume and depends on particle size distribution, shape and cohesiveness of particles Accurately weighed quantityof powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc .

B. Tapped density (D_t)

Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100times from a constant height and tapped volume was read.

It is expressed in gm/cc.

C. **Compressibilityindex:**The compressibility of the powder was determined by the

Carr's compressibility index

D. Hausner ratio: Hausner ratio =tapped density/ bulk density

E. Angle of repose (θ)

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. A funnel was fixed withits tip at a given height(h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel as determined by Fixed funnel method.

2.3.2.Post CompressionParameters[18-20].

A. Thickness and diameter: Controlof physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity.The thickness and diameter of the tablet was measured usingVerniercalipers. It is measured in mm.

B. Hardness: The Mansanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was graduallyincreased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

C. Friability (F)

Tablet strength was tested by Friabilator USPEF-2. Pre-weighed tablets were allowed for 100 revolutions (4min), taken out and were deducted. The percentage weight loss was calculated by rewriting the tablets.

D. Weight variationtest: The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount of drug. The USP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.

E. Uniformity of drug content.: Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in different buffers, the drug content was determined using a UV/Visible Spectrophotometer (PG Instruments).

2.3.3. In-vitro release study:

Table No.2 In-vitro drug release study parameters:

Apparatus	USP XXIV dissolution testing apparatus II (paddle method)
Dissolutionmedium	0.1N HCL, 6.8pH phosphate buffer
Temperature	37 ± 0.5^0 C
RPM	50
Vol. withdrawn and replaced	5ml every 1 hour

λ max	224
Blank solution	Buffers used
Duration of study	12hours
Volume of dissolution media	900ml

Procedure:

The release rate of Miglitol from tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of pH 1.2, for first 2 hours hours and followed by phosphate buffer (pH 6.8; 900 mL) for remaining hours at 37.5±0.5^{0}C and 50 RPM. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with respected dissolution medium. Absorbance of these solutions was measured at 224nm using a UV-Visible Spectrophotometer (PG Instruments). Cumulative percentage of drug release was calculated.

KineticAnalysisofIn-Vitro ReleaseRates ofControlledReleaseTablets[19-20]

The results of in-vitro release profile obtained for all the formulations were plotted in modes of data treatment as Zero – order kinetic model– Cumulative% drug released versus time,First–order kinetic model–Log cumulative percent drug remaining versus time, Higuchi's model–Cumulative percent drug released versus square root of time and Korsmeyer equation/ Peppa's model – Log cumulative percent drug releasedversus logtime.

3. Results and discussion:

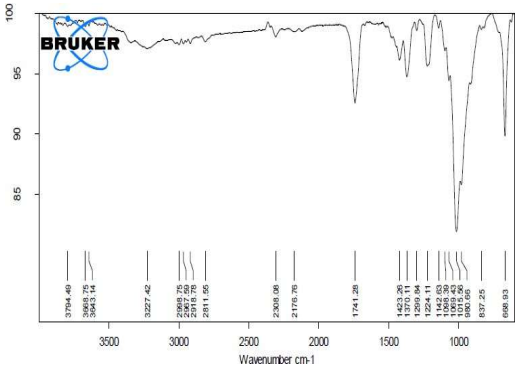
3.1. Preformulation studies:

Solubility: From the solubility studies it was observed that pH1.2 acidic buffer has more solubility than the other buffers as shown in Table.3

Table No.3 Solubility of Miglitol at different pH ranges.

Solvent	% Solubility
Water	0.687
1.2 pH buffer	0.421
7.4 pH buffer	0.659
6.8 pH buffer	0.735

b. Drug- Excipient Compatibility Studies: FTIR Spectra were obtained for Miglitol and polymers of guar gum, Carbopol 934P & Ethylcellulose, the characteristic peaks of the Miglitol werecompared with the peaks obtained for drug and poly-mers and observed that there are no interactions between thepuredrug(Miglitol)andoptimizedformulation(Miglitol+excipients)whichindicatestherearen ophysicalchanges as shown in the figures



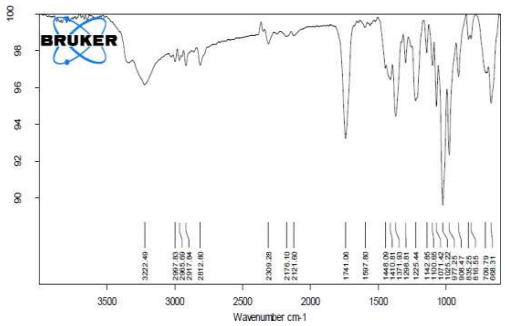


Fig:1IRspectraofPure Miglitol: **Fig:2IRspectraofMiglitolandExcipients**

c. Identification of Miglitol by determination of UV spectrum of Miglitol: From the UV spectral analysis of Miglitol in 10µg/ml it was observed that the Miglitol has 224nm.

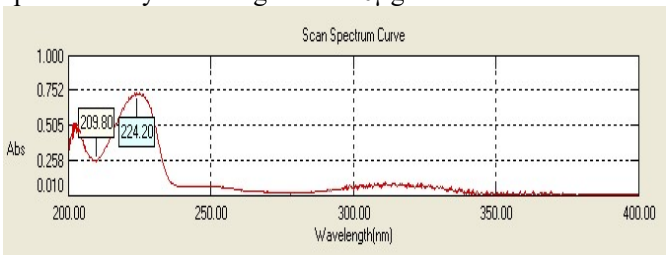
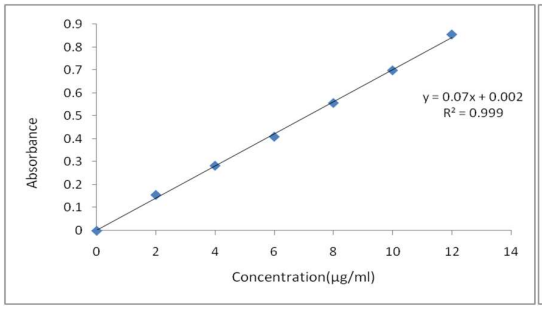


Fig.3 UV spectrum of Miglitol



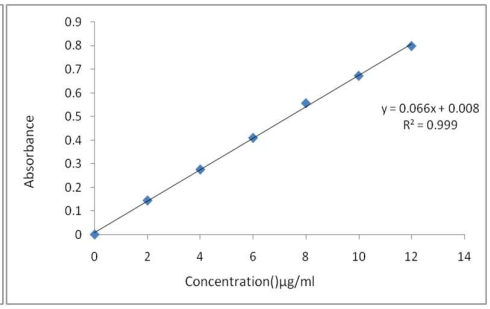


Fig:4Std.CalibrationCurveofMiglitolin pH 1.2: **Fig:5 Std.CalibrationCurveofMiglitolin pH 6.8:**

3.2 CharacterizationofDrug:

Melting Point: Meltingpoint of Miglitolwas determined bycapillarymethod. And wasfoundtobeintherange102-104°Cwhichcompiledwith BPstandards, indicating purityof thedrugsample**.**

EvaluationofMiglitol controlled release matrix Tablets

Table No. 4PreCompressionParameters ofMiglitol controlled release matrix Tablets:

FC	Angle of Repose	Bulk density	Tapped density	Hausners ratio	Carrs index
F1	25.45±0.23	0.332±0.73	0.378±0.54	1.14±0.36	12.17±0.89
F2	28.08±0.45	0.309±0.36	0.356±0.66	1.15±0.37	13.20±0.23
F3	25.46±0.03	0.312±0.83	0.369±0.32	1.18±0.04	15.45±0.43
F4	27.99±0.78	0.305±0.64	0.359±0.67	1.18±0.58	15.04±0.24

F5	25.67±0.46	0.289±0.83	0.325±0.23	1.12±0.34	11.08±0.08
F6	29.09±0.21	0.297±0.78	0.342±0.87	1.15±0.95	13.16±0.56
F7	26.34±0.04	0.289±0.51	0.336±0.47	1.16±0.56	13.99±0.72
F8	27.45±0.56	0.347±0.83	0.397±0.23	1.14±0.59	12.59±0.02
F9	25.89±0.62	0.337±0.74	0.387±0.76	1.15±0.10	12.92±0.28
F10	29.46±0.42	0.312±0.78	0.360±0.97	1.15±0.09	13.33±0.21
F11	27.45±0.68	0.329±0.13	0.385±0.25	1.17±0.68	14.55±0.24
F12	27.23±0.26	0.328±0.90	0.378±0.53	1.15±0.34	13.23±0.48

Table No. 5PostCompressionParameters ofMiglitol controlled release matrix Tablets:Physical properties oftabletformulation(F-1 toF-12):

FC	Avg.Wt (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug Content (%)
F1	149.84	4.26±0.08	7.8±0.02	0.52±0.02	97.26±0.02
F2	149.26	4.28±0.05	6.8±0.25	0.62±0.03	93.25±0.15
F3	148.05	4.98±0.69	8.2±0.31	0.45±0.15	84.63±0.63
F4	150.94	4.29±0.03	7.2±0.02	0.75±0.20	97.52±0.48
F5	151.44	4.3±0.03	8.6±0.03	0.26±0.45	92.36±0.52
F6	147.08	4.29±0.03	8.2±0.36	0.54±0.33	92.56±0.15
F7	148.21	4.41±0.02	9.4±0.41	0.65±0.25	93.21±0.36
F8	149.12	4.44±0.03	7.2±0.02	0.85±0.14	93.15±0.20
F9	150.75	4.28±0.07	7.1±0.06	0.62±0.68	89.18±0.75
F10	149.86	4.32±0.02	7.5±0.21	0.25±0.26	86.84±0.63
F11	151.56	4.34±0.05	8.1±0.23	0.51±0.21	92.15±0.15
F12	149.92	4.33±0.11	8.8±0.08	0.36±0.06	90.24±0.21

The average weight of the Miglitol tablets were found to be in the range of 148.05 to 151.56mg.Thickness of the Miglitol tablets were found to be in the range of 4.26 to 4.52mm.Hardness of the Miglitol tablets were found to be in the range of 6.8 to 9.4kg/cm^2.Friability of the Miglitol tablets were found to be in the range of 0.25 to 0.85% Drug content of the Miglitol tablets were found to be in the range of 84.63 to 97.52%.

3.3 .In-vitro drug releasestudies:

*In-vitro*drugreleasestudieswerecarriedoutusingUSPXXIIdissolutionapparatus typeII(Lab India DS 8000)at50rpm and the dissolutionmediumconsistedof 900mlofbuffer,maintainedat37$\pm$0.5^{0}C.Thedrugreleaseat differenttimeintervalswasmeasuredusinganultravioletvisiblespectrophotometer(PG Instruments) andwas performed in triplicate.

Table No.6 In vitro dissolution studies:

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	46.92	42.53	40.96	36.86	43.68	41.95	32.86	26.84	45.61	39.46	26.06	22.68
2	59.38	62.38	49.35	42.62	62.94	56.35	46.09	29.64	59.38	46.92	39.85	36.05
3	72.68	69.75	57.05	56.38	70.65	69.75	62.64	42.61	66.37	55.49	52.79	43.65
4	98.36	82.64	66.95	69.05	79.35	76.35	69.37	50.38	79.08	63.64	59.42	49.08
6		96.48	80.69	83.46	96.07	82.94	76.34	66.97	86.96	79.04	72.61	65.34
8			92.64	99.38		98.63	80.73	70.34	98.68	93.68	80.69	72.69
10							93.65	82.64			96.15	85.34
12								97.08				92.38

IN VITRO DRUG RELEASE STUDIES:

In Vitro Drug Release Studies of F1-F12 Formulations:

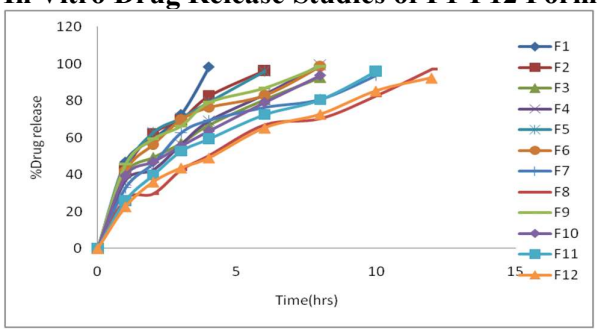
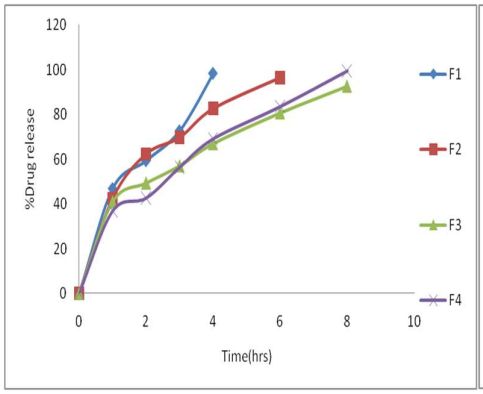


Fig 6:In Vitro Drug Release Studies Of F1-F12 Formulations

In Vitro Drug Release Studies Of F1-F4 & F5-F9 Formulations :



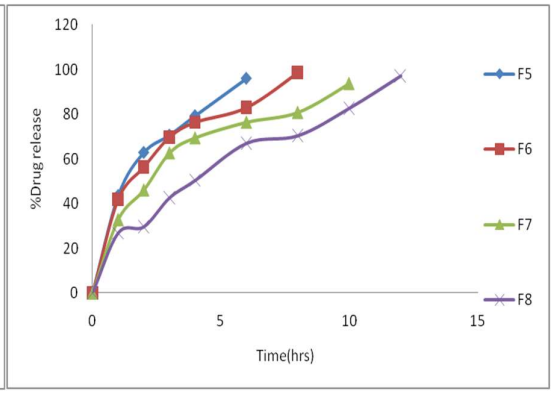


Fig.7 In Vitro Drug Release Studies of F1-F4 Formulations Fig.8: In Vitro Drug Release Studies of F5-F8 Formulations

In Vitro Drug Release Studies Of F9-F12 Formulations:

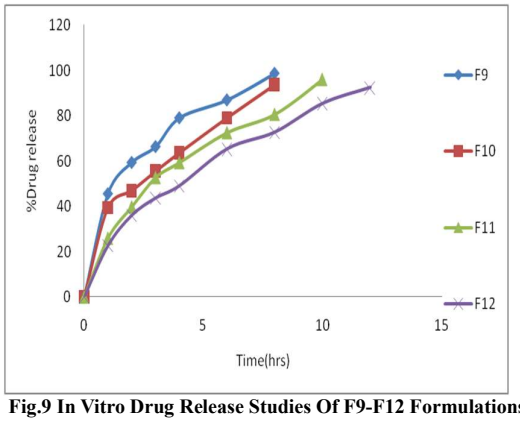


Fig.9 In Vitro Drug Release Studies Of F9-F12 Formulations

Among the all 12 trails F1-F4 trails were formulated using ethyl cellulose in four different ratios the drug release was decreased with increase in the polymer concentration. F1 formulation containing 10mg of Ethyl cellulose shows 98.36% of drug release at the end of 4hours, while F2 formulation containing 20mg of Ethyl cellulose shows 96.48% of drug release at the end of 6hours, whereas F3 formulation containing 30mg of Ethyl cellulose shows 92.34% of drug release at the end of 8hours and F4 formulation containing 40mg of Ethyl cellulose shows 99.38% of drug release at the end of 8hours, Among all the four formulations cant sustained the drug release for 12hours. So further formulations were prepared using Carbopol.

Then F5-F8 trails were formulated using Carbopol in four different ratios like 10, 20, 30, & 40mg the drug release was decreased with increase in the polymer concentration. F5 formulation shows 96.07% of drug release at the end of 6hours, while F6 formulation shows 98.63% of drug release at the end of 8hours, whereas F7 formulation shows 93.65% of drug release at the end of 10 hours and F8 formulation shows 97.08% of drug release at the end of 12hours.

Then F9-F12 trails were formulated using Guar gum in four different ratios like 10, 20, 30, & 40mg. F9 formulation shows 98.68% of drug release at the end of 8hours, while F10 formulation shows 93.68% of drug release at the end of 8hours, whereas F11 formulation shows 96.15% of drug release at the end of 10hours and F12 formulation shows 92.38% of drug release at the end of 12hours.Among the all 12 formulations, based upon the invitro studies F12 formulation containing 40mg of Guar gum choosen as optimized formulation. So the drug release kinetics were performed for the F12 formulation.

3.4.Drug release kinetics:

Zero order kinetics of optimized formulation:

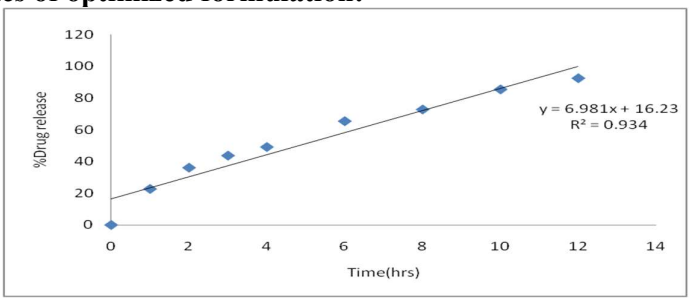


Fig:10.Zero order graph of optimized formulation(F12)

Firstorder kinetics of optimized formulation (F12):

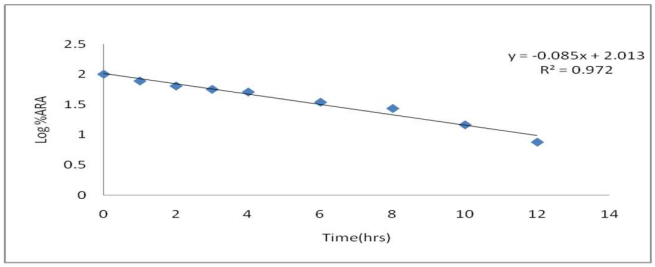


Fig:11.First order graph of optimized formulation

Higuchi plot of optimized formulation (F12):

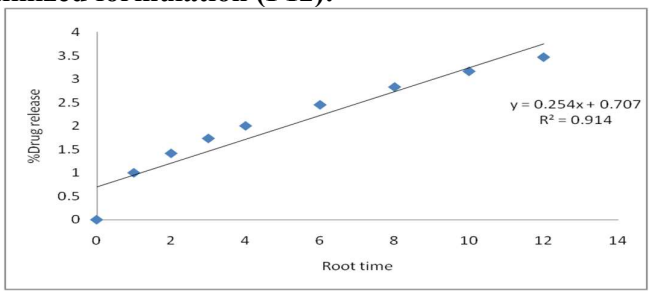


Fig:12.Higuchi graph of optimized formulation

Peppas plot plot of optimized formulation (F12):

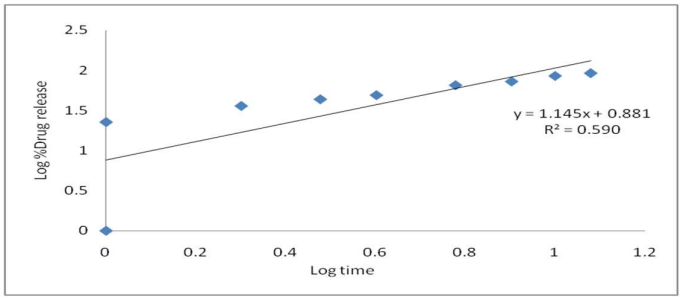


Fig:13.Peppas graph of optimized formulation

Table7:Drug release kinetics:

	R^2 values				n values
Formulation	**Zero order**	**First order**	**Higuchi**	**Korsmeyer - Peppas**	**Korsmeyer-Peppas (n)**
F12	**0.934**	**0.972**	**0.914**	**0.590**	**1.145**

The in-vitro dissolution data for best formulation F12 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F12 shows R^2 value 0.972. As its value nearer to the '1' it is conformed as it follows the First order release. The mechanism of drug release is further confirmed by the korsmeyer and

peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport.

The 'n' value is 1.145 for the optimised formulation (F12) i.e., n value was n > 0.89 this indicates Super case II transport. The release kinetics for the optimized formula are shown in table.

4. Conclusion:

Inthisstudy controlled release matrixtabletsofMiglitolwerepreparedby Direct compression method,using ethyl cellulose,Guar gumandcarbopolpolymersasretardant. The pre compression and post compression parameters show that the values were found to be acceptable within the range.Among the all 12 formulations F12 formulation containing 40mg of guar gum controls the drug release upto 12hours. So guar gum was considered to be suitable for the formulation of Miglitol controlled release tablets at 40mg. BasedontheseresultsformulationF12 wasfoundtobe themostpromisingformulations.Theregressioncoefficient(R^2)ofHiguchiplotof Optimized formulation F12 shows R^2 value 0.972. As its value nearer to the '1' it is conformed as it follows the first order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot.

5. Acknowledgement: -

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