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Formulation and *invitro* evaluation of controlled release matrix tablets of miglitol

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ABSTRACT

Oral controlled drug delivery systems have received much attention of the researchers during the past two decades. The rationale for developing a controlled release formulation is to enhance its therapeutic benefits, reducing its side effects and improving the management of diseased condition. Studies have been carried out for developing oral controlled release matrix tablet formulations of Miglitol by using polymeric materials like Tragacanth, Chitosan and Acacia Gum. FTIR Spectral studies shown that drug and excipients used were compatible with each other. All the formulations were passed various physicochemical evaluation parameters such as Angle of Repose, Bulk Density, Tapped Density, Carr's Index, Hausners Ratio and Post Compression parameters Weight Variation, Hardness, Thickness, Friability and Drug Content. From the dissolution studies it was evident that the formulation F5 showed better and desired drug release pattern i.e., 99.35 % in 12 hours. It contains the Chitosan as polymer. It followed Zero order kinetics.

Keywords: Miglitol, Tragacanth, Chitosan and Acacia Gum and Controlled release tablets.

INTRODUCTION

Over the Past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention is being paid on development of oral controlled release drug delivery systems. The goal in designing controlled release drug delivery system is to reduce the frequency of the dosing, reducing the dose and providing uniform drug delivery. So, controlled release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. Controlled release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.[1]

The Important role of novel drug delivery system that improve the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and or targeting the drug to desired site. The aim of any drug delivery system is to provide a therapeutic amount of drug to the specific site in the body to achieve promptly and then maintain the desired drug concentration.[2,3] The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system includes any drug delivery systems that achieves slow release of drug over prolong period of time.[4] Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables,utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipient by matrix based formulation. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patients, discovery of new polymeric materials suitable for prolonging the drug release, and the

improvement in therapeutic efficiency and safety achieved by these delivery systems. Now days the technology of sustained release is also being applied to veterinary products also.[5]

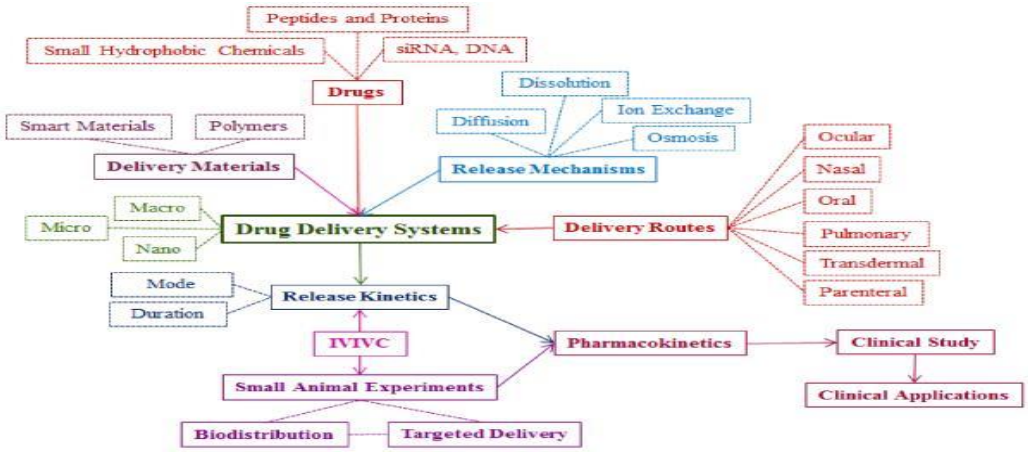


Fig 1: Drug delivery system

DRAWBACK OF CONVENTIONAL DOSAGE FORM

1) Poor patient compliance: Chances of missing of the dose of a drug.
2) The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of Drawback of conventional dosage form.
4) The fluctuations in drug levels which causes precipitation of adverse effects mainly the drug which having the small Therapeutic Index whenever over medication occur.[6,7,8]

ADVANTAGES

i) Patient compliance: Lack of compliance is mainly observed with chronic disease which required long term treatment, as success of drug therapy depends on the patient ability to comply with the drug treatment. Patient compliance is affected by a various factors, like knowledge of disease process, patient faith in treatment, and understanding of patient related to a strict treatment schedule. Also the complication of therapeutic regimens, the cost of therapy and local or systemic side effect of the dosage form. This problem can be resolved to some extent by administering sustained release drug delivery system.

ii) Reduced 'see-saw' fluctuation: Drug concentration in the systemic circulation and tissue compartments show 'see saw' pattern frequently when the drug administration in conventional dosage form. The magnitudes of these fluctuations mainly depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' pattern is more prominent just in case of drugs with biological half-life less than four hours, since recommended dosing intervals are rarely less than four hours. A well designed sustained release drug delivery system can widely reduce the frequency of drug dosing and also mainta in a steady drug concentration in blood circulation and target tissue cells.

iii) Total dose reduction: To treat a diseased condition less amount of total drug is used in Sustained release drug delivery systems. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

iv) Improvement of deficiency in treatment: Optimal therapy of a disease requires an effective transfer of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A sustained release dosage form leads to better management of the acute or chronic disease condition.

v) Economy: The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over an prolong period of time may be less.[9,10]

MATERIALS AND METHODS

Miglitol Provided by SURA LABS, Dilsukhnagar, Hyderabad. Tragacanth from Loba Chemie Pvt Ltd Mumbai, India. Chitosan from Merck Specialities Pvt Ltd, Mumbai, India. Acacia Gum from Aravind Remedies (AR), Chennai, India. PVP K30 from Unify chemicals, Jothi Aromas from DK Enterprises, India. MCC PH 101 from S.D. Fine Chemicals. India. Magnesium from stearate Merck Specialities Pvt Ltd, Mumbai, India. Talc from Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY

Analytical method development

a) Determination of absorption maxima

100mg of Miglitol pure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl

(10µg/ml) and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve

100mg of Miglitol pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 10, 20, 30, 40 and 50µg/mL of Miglitol per ml of solution. The absorbance of the above dilutions was measured at 215nm 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. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Preformulation parameters

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.

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 1. The tablets were prepared as per the procedure given below and aim is to prolong the release of Miglitol Total weight of the tablet was considered as 150mg.

Procedure

1) Miglitol 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.

Table 1: Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION CODE								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Miglitol	25	25	25	25	25	25	25	25	25
Tragacanth	25	50	75	-	-	-	-	-	-
Chitosan	-	-	-	25	50	75	-	-	-
Acacia Gum	-	-	-	-	-	-	25	50	75
PVP K30	10	10	10	10	10	10	10	10	10
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	4	4	4	4	4	4	4	4	4
MCC PH 101	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total tablet weight	150	150	150	150	150	150	150	150	150

All the quantities were in mg

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

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

Table 2: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

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
Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug 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 media. 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 drug release studies
Dissolution parameters
Apparatus --USP-II, Paddle Method
Dissolution Medium --0.1 N HCl, pH 6.8 Phosphate buffer
RPM --50
Sampling intervals (hrs)--0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12
Temperature --37°C $\pm$ 0.5°C

Procedure
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 apparatus was operated for 2 hours and then the media 0.1 N HCl were removed and pH 6.8 phosphate buffer was added process was continued from up to 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 215 and 218nm using UV-spectrophotometer.

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.

Drug – Excipient compatibility studies
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 Agilent spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1}. The resultant spectrum was compared for any spectrum changes.

RESULTS AND DISCUSSION

Standard Calibration curve of Miglitol

Table 3: Concentration and absorbance obtained for calibration curve of Miglitol in 0.1 N hydrochloric acid buffer (pH 1.2)

S. No.	Concentration (µg/ml)	Absorbance* (at 215 nm)
1	0	0
2	10	0.159
3	20	0.264
4	30	0.384
5	40	0.521
6	50	0.641

It was found that the estimation of Miglitol by UV spectrophotometric method at λ_{max} 215 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 10-50µg/ml.

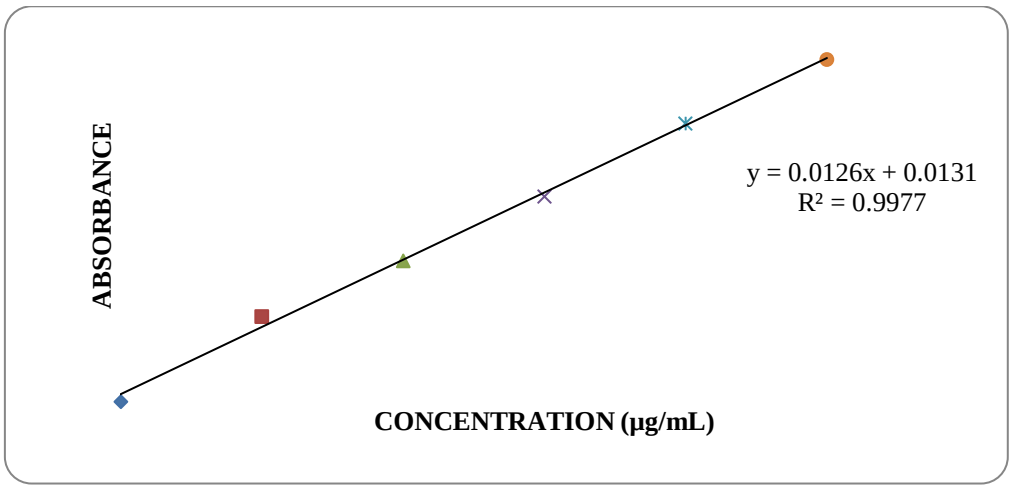


Fig 2: Standard graph of Miglitol in 0.1 N HCl

Table 4: Concentration and absorbance obtained for calibration curve of Miglitol in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 218 nm)
1	0	0
2	10	0.132
3	20	0.244
4	30	0.374
5	40	0.498
6	50	0.609

It was found that the estimation of Miglitol by UV spectrophotometric method at λ_{max} 218 nm in pH 6.8 Phosphate buffer. It had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 10-50µg/ml.

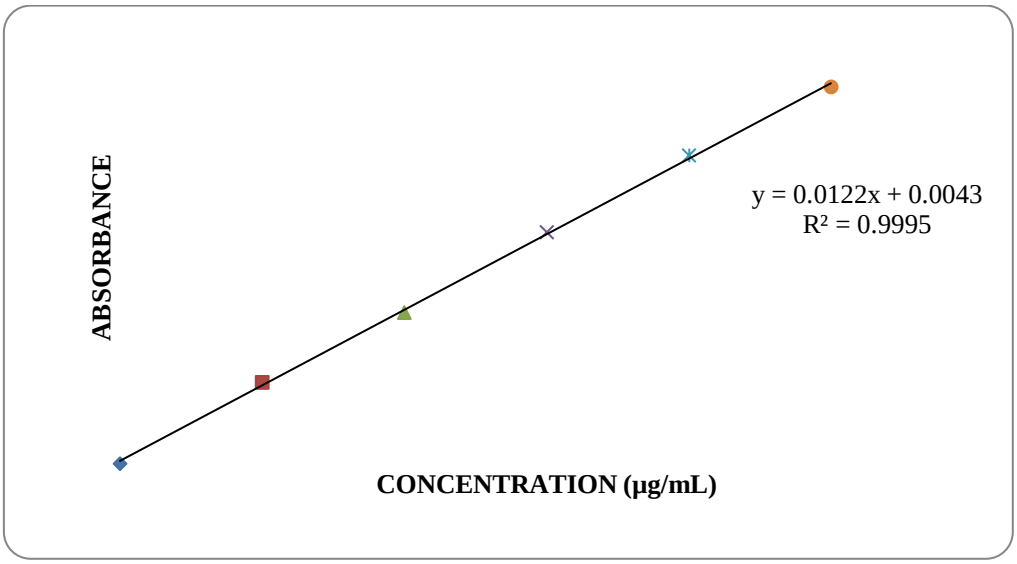


Fig 3: Standard graph of Miglitol in pH 6.8 Phosphate buffer

Evaluation Parameters for sustained release tablets of Miglitol

Pre-compression parameters

The data's were shown in Table 5.The values for angle of repose were found in the range of 19.35°-21.20°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.392±0.29 to 0.514±0.34 (gm/cc) and 0.439±0.25 to 0.672±0.29 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 12.06±0.27 % to 13.54±0.29 %. The Hausner ration fall in range of 1.014±0.25 to 1.152±0.16. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 5: Pre-compression parameters					
Formulation Code	**Angle of Repose**	**Bulk density (gm/ml)**	**Tapped density (gm/ml)**	**Carr's index (%)**	**Hausner's Ratio**
F1	19.89±0.35	0.461±0.25	0.581±0.35	13.28±0.23	1.039±0.13
F2	19.61±0.32	0.460±0.39	0.563±0.33	13.54±0.29	1.054±0.19
F3	20.80±0.51	0.514±0.34	0.672±0.29	12.39±0.19	1.116±0.21
F4	21.20±0.18	0.464±0.36	0.591±0.32	13.20±0.27	1.152±0.16
F5	20.7±0.42	0.432±0.14	0.573±0.28	12.69±0.26	1.049±0.13
F6	19.69±0.25	0.414±0.17	0.530±0.18	12.06±0.27	1.028±0.26
F7	21.02±0.23	0.484±0.14	0.546±0.26	12.86±0.41	1.121±0.24
F8	20.61±0.26	0.392±0.29	0.439±0.25	12.32±0.37	1.062±0.26
F9	19.35±0.14	0.457±0.26	0.586±0.31	12.21±0.31	1.014±0.25

Post compression Parameters

Weight variation: Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 6. The average weight of the tablet is approximately in range of 147.99 to 150.27 mg, so the permissible limit is ±5% (150 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test: Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 6. The results showed that the hardness of the tablets is in range of 4.6 to 5.6 kg/cm^2, which was within IP limits.

Thickness: Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-6 The result showed that thickness of the tablet is raging from 3.02 to 3.62 mm.

Friability: Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 8.4. The average friability of all the formulations lies in the range of 0.31 to 0.62 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 95.98 – 99.36 %.

Table 6 : post compression parameter					
Formulations	**Weight variation (mg)**	**Hardness (kg/cm^2)**	**Thickness (mm)**	**Friability (%)**	**Drug content (%)**
F1	149.34	5.3	3.15	0.50	98.54
F2	150.19	5.0	3.62	0.42	96.46
F3	148.97	5.1	3.02	0.31	98.78
F4	150.24	5.6	3.14	0.62	99.36
F5	147.99	5.0	3.25	0.59	96.49
F6	150.03	4.9	3.42	0.42	98.72
F7	149.72	5.3	3.51	0.56	97.57
F8	150.27	5.0	3.19	0.45	95.98
F9	149.83	4.6	3.34	0.38	98.20

In-Vitro Dissolution studies

In-Vitro dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 12 hours. The samples were withdrawn at regular time intervals of 30 min,1 hour,2 hr,3,5,5,6,7,8,9, 10,11 and 12 hours respectively. The results were displayed in table 7.

Table 7: *In -vitro* dissolution data

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.47	25.89	10.15	15.56	14.24	16.31	21.16	19.93	17.24
2	26.35	31.93	16.29	20.82	18.81	20.42	29.47	26.40	30.63
3	31.12	42.52	23.31	28.86	23.92	27.69	34.15	31.96	36.42
4	38.86	48.17	30.55	33.35	30.23	33.34	42.74	39.12	45.90
5	46.90	53.75	36.90	38.16	36.56	38.29	49.81	43.80	48.74
6	52.63	59.53	41.21	42.10	45.60	42.14	58.27	47.10	55.45
7	60.52	64.98	49.18	47.57	50.98	58.28	69.10	50.62	60.27
8	75.71	70.16	58.63	66.76	57.71	63.95	76.43	56.34	67.10

9	85.18	75.24	61.71	70.42	62.25	70.24	82.91	60.15	75.72
10	96.63	83.13	76.82	85.93	74.16	75.32	89.19	73.27	83.16
11		97.19	90.49	98.84	82.53	87.41	95.87	83.92	89.47
12			98.17		99.35	96.35		90.20	94.18

From the dissolution data it was evident that the formulations prepared with Tragacanth as polymer were able to retard the drug release up to desired time period i.e., 12 hours.

The formulations prepared with Chitosan were showed maximum retarded the drug release. When the polymer concentration was increased drug release was decreased.

Whereas the formulations prepared with Acacia Gum were retarded the drug release in the concentration of 75 mg (F9 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 94.18 % in 12 hours with good retardation.

From the above results it was evident that the formulation F5 is best formulation with desired drug release pattern extended up to 12 hours.

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 mode.

Table 8: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
14.24	1	1.000	1.154	0.000	1.933	14.240	0.0702	-0.846	85.76	4.642	4.410	0.232
18.81	2	1.414	1.274	0.301	1.910	9.405	0.0532	-0.726	81.19	4.642	4.330	0.311
23.92	3	1.732	1.379	0.477	1.881	7.973	0.0418	-0.621	76.08	4.642	4.237	0.404
30.23	4	2.000	1.480	0.602	1.844	7.558	0.0331	-0.520	69.77	4.642	4.117	0.525
36.56	5	2.236	1.563	0.699	1.802	7.312	0.0274	-0.437	63.44	4.642	3.988	0.653
45.6	6	2.449	1.659	0.778	1.736	7.600	0.0219	-0.341	54.4	4.642	3.789	0.853
50.98	7	2.646	1.707	0.845	1.690	7.283	0.0196	-0.293	49.02	4.642	3.660	0.982
57.71	8	2.828	1.761	0.903	1.626	7.214	0.0173	-0.239	42.29	4.642	3.484	1.158
62.25	9	3.000	1.794	0.954	1.577	6.917	0.0161	-0.206	37.75	4.642	3.355	1.287
74.16	10	3.162	1.870	1.000	1.412	7.416	0.0135	-0.130	25.84	4.642	2.956	1.685
82.53	11	3.317	1.917	1.041	1.242	7.503	0.0121	-0.083	17.47	4.642	2.595	2.047
99.35	12	3.464	1.997	1.079	-0.187	8.279	0.0101	-0.003	0.65	4.642	0.866	3.775

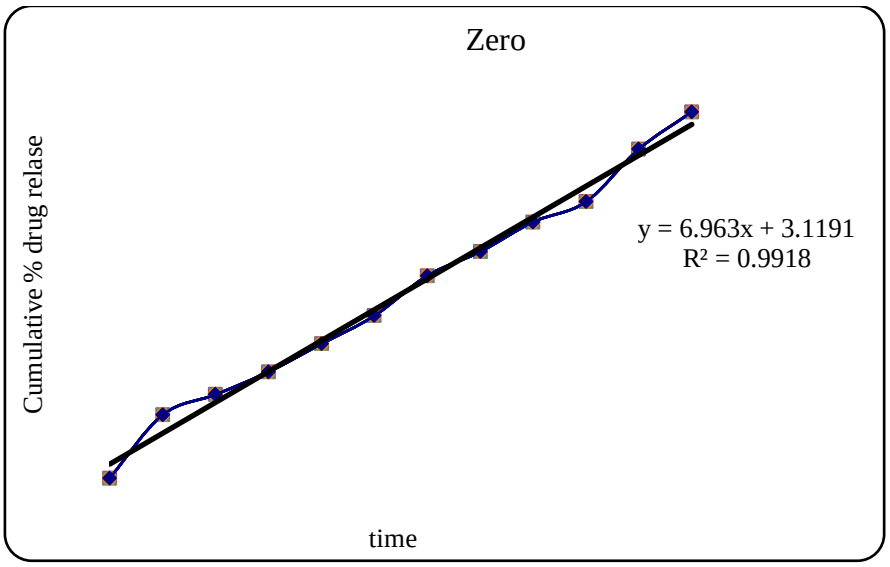


Fig 4 : Zero order release kinetics graph

From the above graphs it was evident that the formulation F5 was followed **Zero order kinetics** mechanism.

FTIR

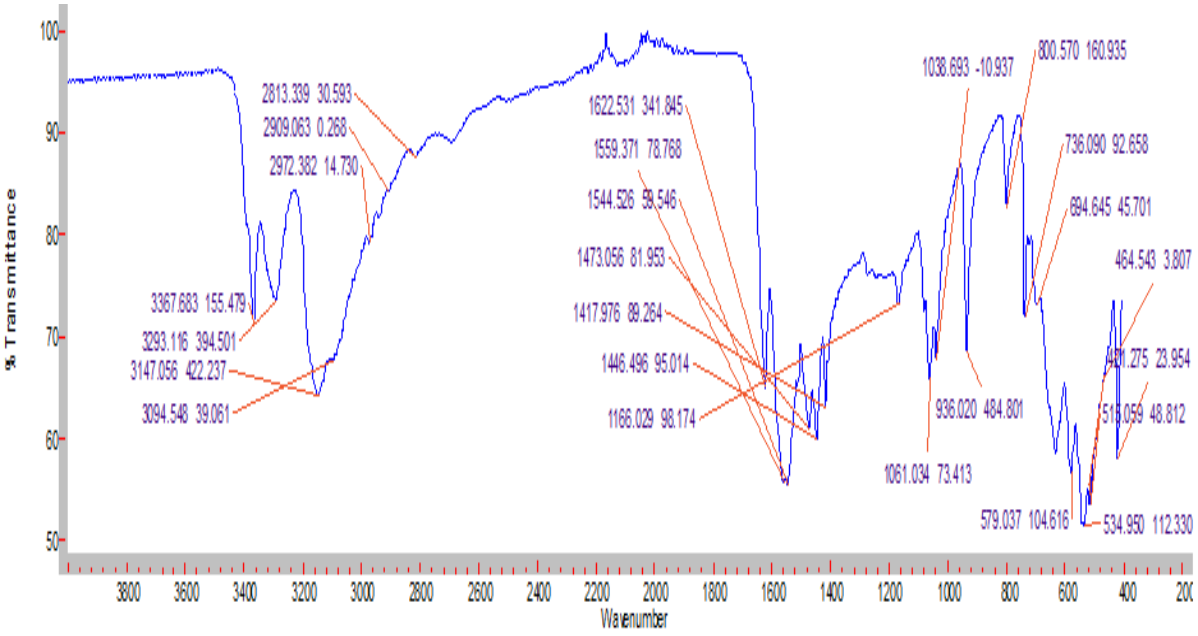
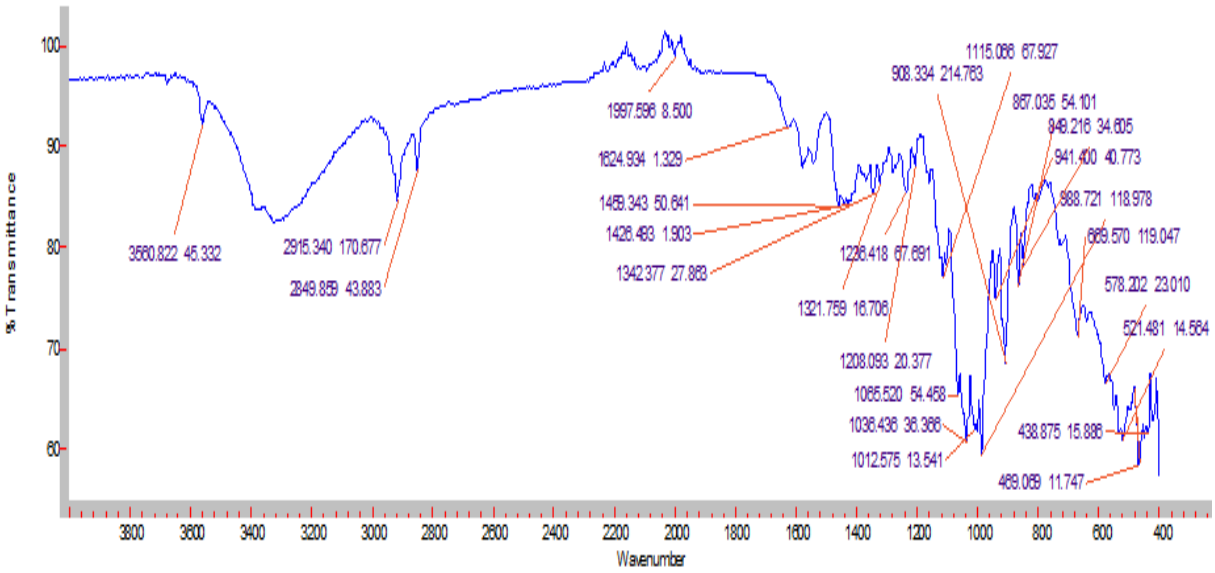


Fig 5: FT-TR Spectrum of Miglitol pure drug



There is no incompatibility of pure drug and excipients. There is no disappearance of peaks of pure drug and in optimised formulation.

Fig 6: FT-IR Spectrum of Optimised Formulation

CONCLUSION

In the present work, an attempt has been made to develop Controlled release tablets of Miglitol by selecting different Types of polymers Tragacanth, Chitosan and Acacia Gum as retarding. All the formulations were prepared by direct compression method. FTIR spectral studies of selected formulations of Miglitol exhibited no major interactions between the drug, polymer and diluents. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation showed maximum % drug release i.e., 99.35 % in 12 hours hence it is considered as optimized formulation F5 which contains Chitosan (50mg). Whereas the formulations with Chitosan showed high retarding with increasing concentration of polymer. The drug release kinetics showed Zero order.

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