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Formulation and in-vitro evaluation of controlled release tablets of miglitol

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ABSTRACT

The aim of the present study was to develop and evaluate the controlled release tablets by using direct compression method of Miglitol tablet. Controlled release tablets were prepared by employing Sodium alginate, Carbopol 971P and Ethyl cellulose at different concentration. Flow properties – Angle of repose, loose bulk density, tapped density and also % Carr's compressibility was determined for all the formulations which showed good flow property. The thickness found uniform, hardness and friability values of all the formulation tablets prepared by direct compression method were within the limits and found to be mechanically stable. *In vitro* dissolution results showed that % of drug release was prolonged in formulation M4 that is up to 12 hours when compared to other formulations. This indicates that the drug released from the formulation M4 was effective up to 12 hours.

Keywords: Miglitol, Sodium alginate, Carbopol 971P, Ethyl cellulose, direct compression method and Controlled release tablets.

INTRODUCTION

Controlled release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

The first Controlled release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Controlled release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing Controlled or Controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, Controlled release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ.

Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is Controlled on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as Controlled release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and

proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of Controlled release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of Controlled release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the Controlled release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

Rationale for extended release dosage forms

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose . However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period..

The Controlled plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well.

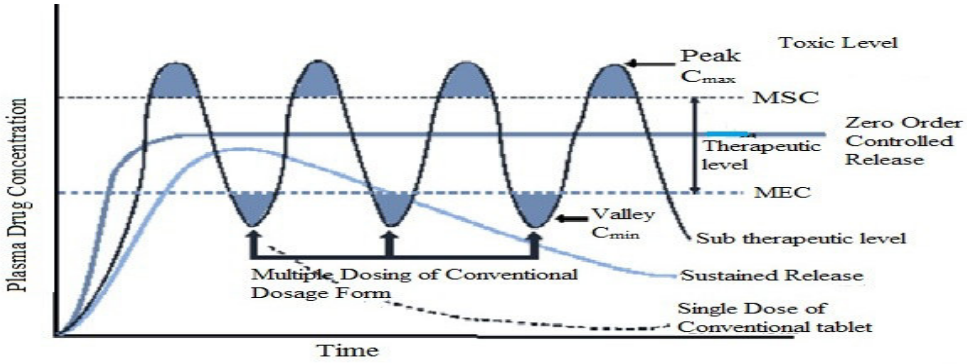

Figure 1: Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of Controlled and controlled delivery formulations.

Drawbacks of Conventional Dosage Forms

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
3. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

Aim and objective

Aim of the Work

Aim of the study is to formulate and evaluate Miglitol Controlled release tablets by using polymers such as Sodium alginate, Carbopol 971P and Ethyl cellulose.

Objective of the Study

- ✓ To formulate controlled release tablets of Miglitol for the treatments of diabetes mellitus type 2.
- ✓ To formulate Controlled release tablets by using different types of polymers like Sodium alginate, Carbopol 971P and Ethyl cellulose.
- ✓ To evaluate pre and post compression evaluation parameters
- ✓ To perform Drug and Excipient compatibility studies (FTIR)
- ✓ To formulate Miglitol Controlled release tablets for the improvement of Bioavailability.
- ✓ To perform various quality control evaluation parameters for the prepared tablets.

Miglitol is an oral anti-diabetic drug that acts by inhibiting the ability of the patient to break down 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 monosaccharides which can be absorbed by the body.

The main objective of this study is to extend the drug release there by reducing the frequency of dosage.

MATERIALS AND METHOD MATERIALS

Miglitol was Provided by SURA LABS, Dilsukhnagar, Hyderabad . Sodium alginate ,Carbopol 971P ,Talc , PVP K30 and MCC was gift sample from Merck Specialities Pvt Ltd, Mumbai, India , I Ethyl cellulose was purchased from Colorcon asia private Ltd. Goa, India , Magnesium Stearate was purchased from Sri Krishna Pharmaceuticals Ltd, India

Methodology

Table 1: Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION CODES								
	M1	M2	M3	M4	M5	M6	M7	M8	M9
Miglitol	25	25	25	25	25	25	25	25	25
Sodium alginate	25	50	75	-	-	-	-	-	-
Carbopol 971P	-	-	-	25	50	75	-	-	-
Ethyl cellulose	-	-	-	-	-	-	25	50	75
Talc	4	4	4	4	4	4	4	4	4
Magnesium Stearate	5	5	5	5	5	5	5	5	5
PVP K30	10	10	10	10	10	10	10	10	10
MCC	81	56	31	81	56	31	81	56	31
Total weight	150	150	150	150	150	150	150	150	150

RESULTS AND DISCUSSION

The present study was aimed to developing controlled release tablets of miglitol using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

A graph of Miglitol was taken in simulated gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 238 nm and 240 nm respectively.

Table 2: Observations for graph of Miglitol in 0.1N HCl (238)

Concentration (µg/ml)	Absorbance
0	0
2	0.132
4	0.239
6	0.355
8	0.471
10	0.586

It was found that the estimation of Miglitol by UV spectrophotometric method at λ_{max} 238.0 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, 2-10µg/ml. The regression equation generated was y = 0.058x+0.007

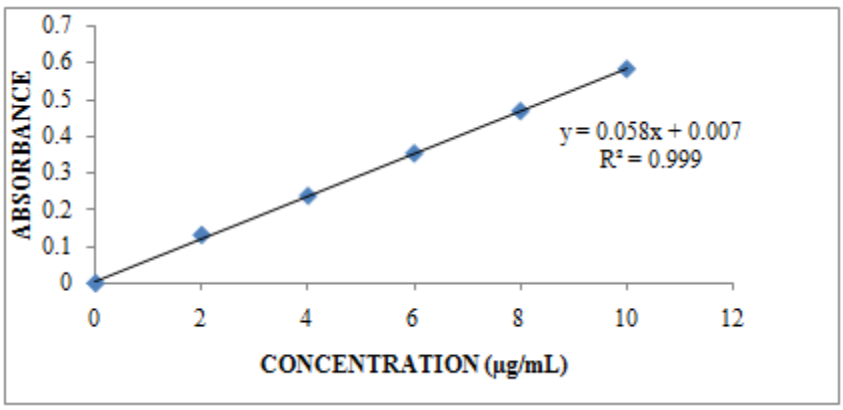

Figure 2: Standard graph of Miglitol in 0.1N HCl

Table 3: Observations for graph of Miglitol in pH 6.8 phosphate buffer (240nm)

Concentration (µg/ml)	Absorbance
0	0
2	0.169
4	0.322
6	0.478
8	0.622
10	0.764

It was found that the estimation of Miglitol by UV spectrophotometric method at λ_{max} 240 nm in pH 6.8 Phosphate buffer 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, 2-10µg/ml. The regression equation generated was y = 0.076x + 0.011.

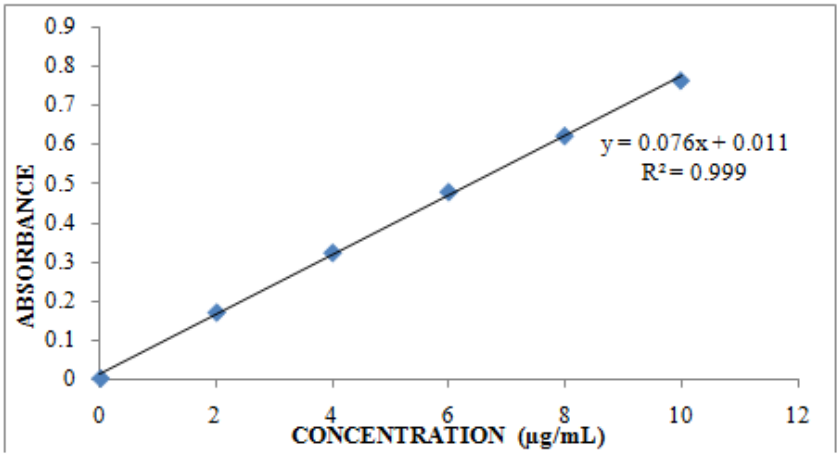

Figure 3: Standard graph of Miglitol pH 6.8 phosphate buffer (240nm)

Preformulation parameters of powder blend

Table 4: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's Ratio
M1	24.45□±□0.03	0.58□±□0.04	0.66□±□0.02	12.12□±□0.35	1.08
M2	24.49□±□0.01	0.58□±□0.02	0.66□±□0.08	12.12□±□1.55	1.17
M3	24.51□±□0.02	0.62□±□0.04	0.67□±□0.04	7.46□±□1.36	1.07
M4	24.17□±□0.05	0.61□±□0.04	0.69□±□0.06	11.59□±□1.11	1,10
M5	24.42□±□0.01	0.60□±□0.03	0.69□±□0.02	13.04□±□1.05	1.10
M6	24.62□±□0.03	0.58□±□0.05	0.66□±□0.07	12.12□±□1.27	1.07
M7	26.57□±□0.02	0.56□±□0.05	0.65□±□0.04	13.84□±□0.35	1.08
M8	27.09□±□0.03	0.57□±□0.09	0.66±0.08	13.63□±□1.01	1.10
M9	27.06□±□0.02	0.58□±□0.06	0.66□±□0.07	12.12□±□1.13	1.11

Quality control parameters for tablets

Tablet quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Table: 5 *In vitro* quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
M1	148.25	5.36	0.36	3.57	98.48
M2	146.34	5.12	0.47	3.95	99.12
M3	149.20	5.92	0.82	3.14	96.35
M4	147.98	5.30	0.16	3.82	98.02

M5	150.03	5.71	0.75	3.80	99.37
M6	148.78	5.95	0.62	3.73	97.84
M7	147.12	5.50	0.47	3.56	98.15
M8	149.35	5.14	0.29	3.68	98.36
M9	149.93	5.28	0.36	3.46	96.20

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

In Vitro Drug Release Studies

Table 6: Dissolution data of Miglitol tablets

TIME (H)	CUMULATIVE PERCENTAGE OF DRUG RELEASED								
	M1	M2	M3	M4	M5	M6	M7	M8	M9
0	0	0	0	0	0	0	0	0	0
0.5	11.98	10.24	13.31	19.19	07.82	10.20	18.01	13.92	10.87
1	18.25	16.83	19.28	23.52	12.93	15.35	23.11	17.53	15.04
2	28.54	23.96	25.10	28.63	17.52	21.15	30.29	28.14	20.17
3	35.12	28.15	31.71	35.92	24.14	28.96	40.63	35.05	26.32
4	43.23	38.71	36.86	41.05	30.72	36.72	46.82	42.98	32.15
5	50.85	47.10	40.25	47.10	36.89	42.54	51.90	47.11	38.21
6	56.14	53.06	48.93	53.59	45.21	47.92	58.14	56.70	42.76
7	63.60	57.24	59.24	59.65	50.63	54.75	66.27	63.38	50.25
8	78.14	69.59	65.12	66.24	57.89	62.40	71.86	72.25	55.93
9	86.78	76.67	70.93	73.12	61.11	68.63	85.52	78.91	67.42
10	96.65	85.18	75.41	88.78	66.05	73.99	96.46	86.63	74.08
11		98.27	82.98	93.39	79.93	76.12		98.34	77.50
12			90.42	99.56	87.36	80.76			89.68

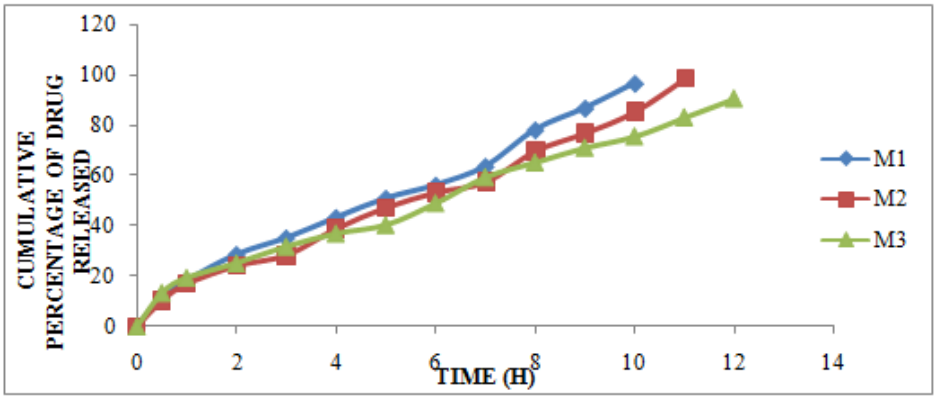

Fig 4: Dissolution profile of Miglitol (M1, M2, and M3 formulations)

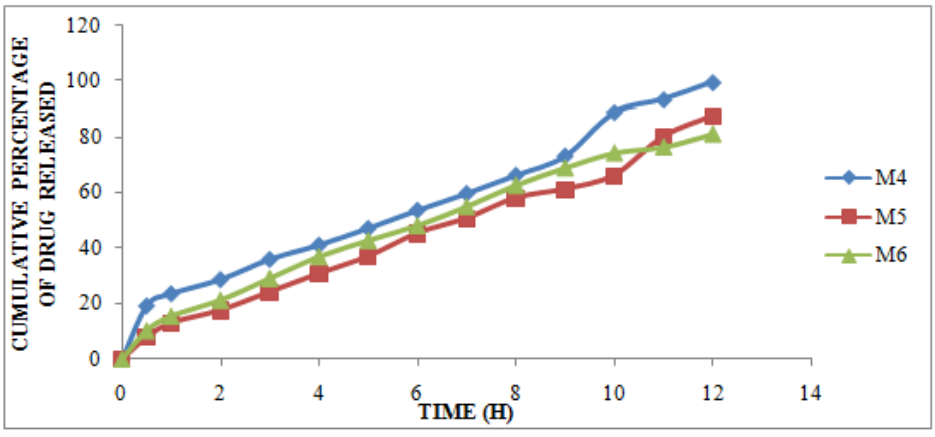

Fig 5: Dissolution profile of Miglitol (M4, M5 and M6 formulations)

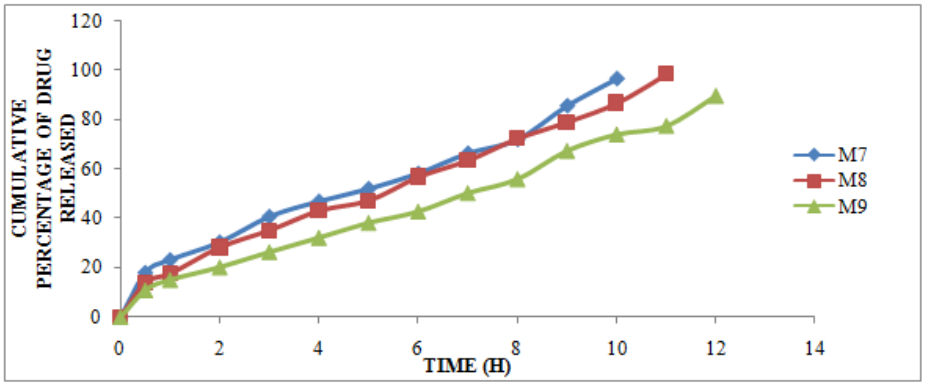

Fig 6: Dissolution profile of Miglitol (M7, M8 and M9 formulations)

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.

Table 7: 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
19.19	0.5	0.707	1.283	-0.301	1.907	38.380	0.0521	-0.717	80.81	4.642	4.323	0.318
23.52	1	1.000	1.371	0.000	1.884	23.520	0.0425	-0.629	76.48	4.642	4.245	0.397
28.63	2	1.414	1.457	0.301	1.854	14.315	0.0349	-0.543	71.37	4.642	4.148	0.494
35.92	3	1.732	1.555	0.477	1.807	11.973	0.0278	-0.445	64.08	4.642	4.002	0.640
41.05	4	2.000	1.613	0.602	1.770	10.263	0.0244	-0.387	58.95	4.642	3.892	0.750
47.1	5	2.236	1.673	0.699	1.723	9.420	0.0212	-0.327	52.9	4.642	3.754	0.888
53.59	6	2.449	1.729	0.778	1.667	8.932	0.0187	-0.271	46.41	4.642	3.594	1.048
59.65	7	2.646	1.776	0.845	1.606	8.521	0.0168	-0.224	40.35	4.642	3.430	1.212
66.24	8	2.828	1.821	0.903	1.528	8.280	0.0151	-0.179	33.76	4.642	3.232	1.410
73.12	9	3.000	1.864	0.954	1.429	8.124	0.0137	-0.136	26.88	4.642	2.996	1.646
88.78	10	3.162	1.948	1.000	1.050	8.878	0.0113	-0.052	11.22	4.642	2.239	2.403
93.39	11	3.317	1.970	1.041	0.820	8.490	0.0107	-0.030	6.61	4.642	1.877	2.765
99.56	12	3.464	1.998	1.079	-0.357	8.297	0.0100	-0.002	0.44	4.642	0.761	3.881

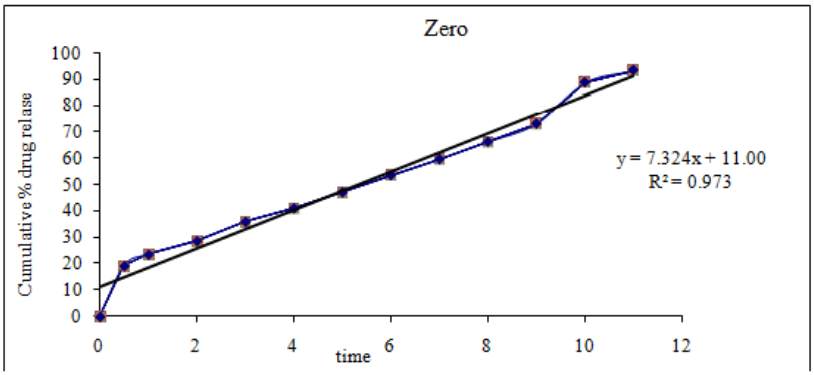

Fig 7: Zero order release kinetics graph

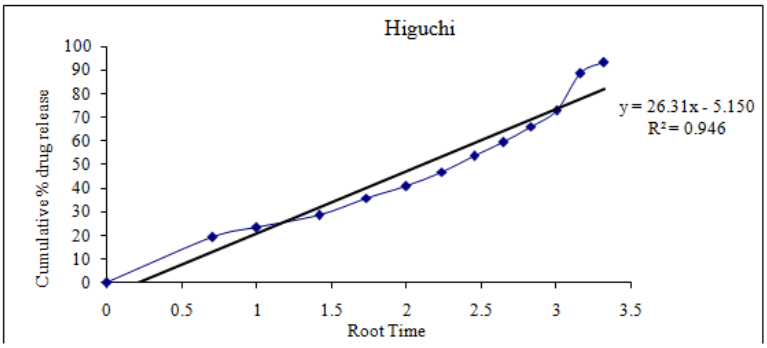

Fig 8 : Higuchi release kinetics graph

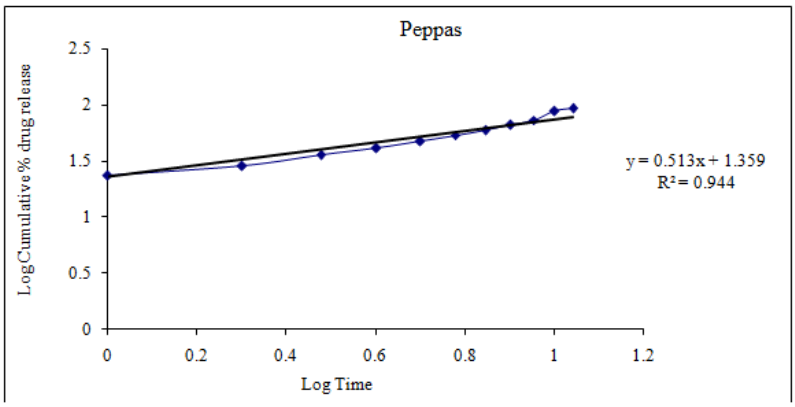

Fig 9: Kars mayer peppas graph

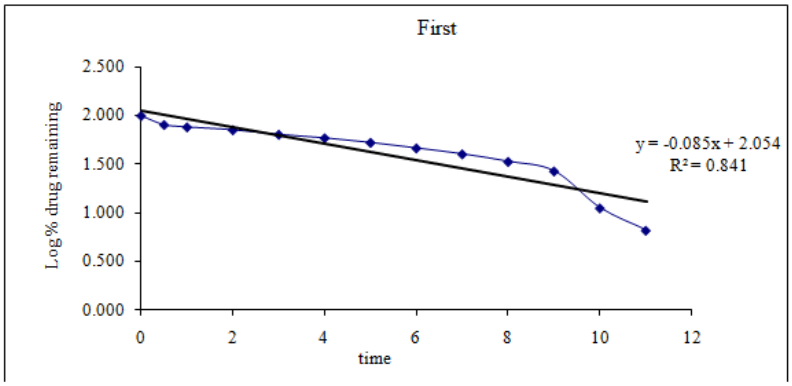

Fig 10: First order release kinetics graph

From the above graphs it was evident that the formulation M4 was followed Zero order release kinetics.

Drug – Excipient compatability studies
Fourier Transform-Infrared Spectroscopy

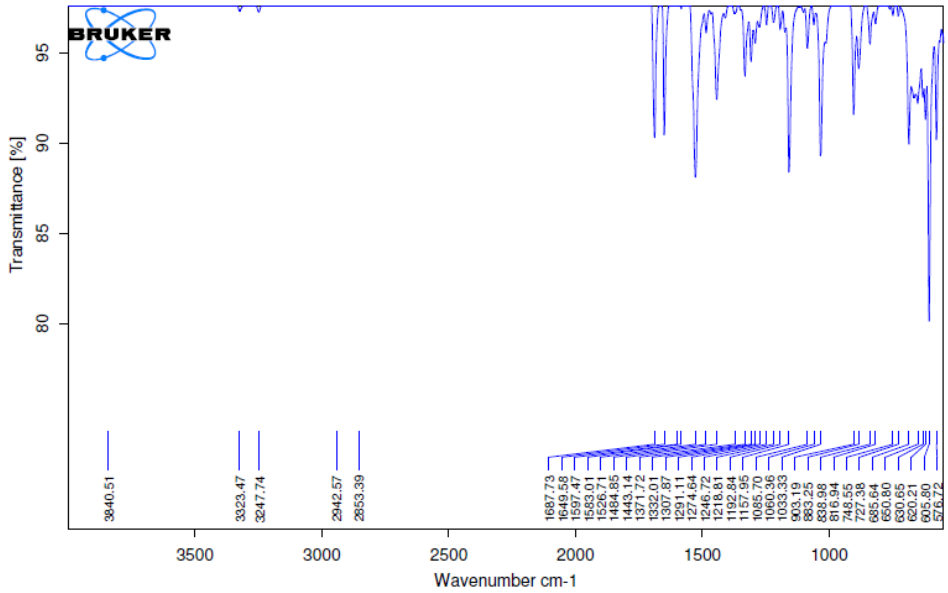

Figure 11: FT-IR Spectrum of Miglitol pure drug

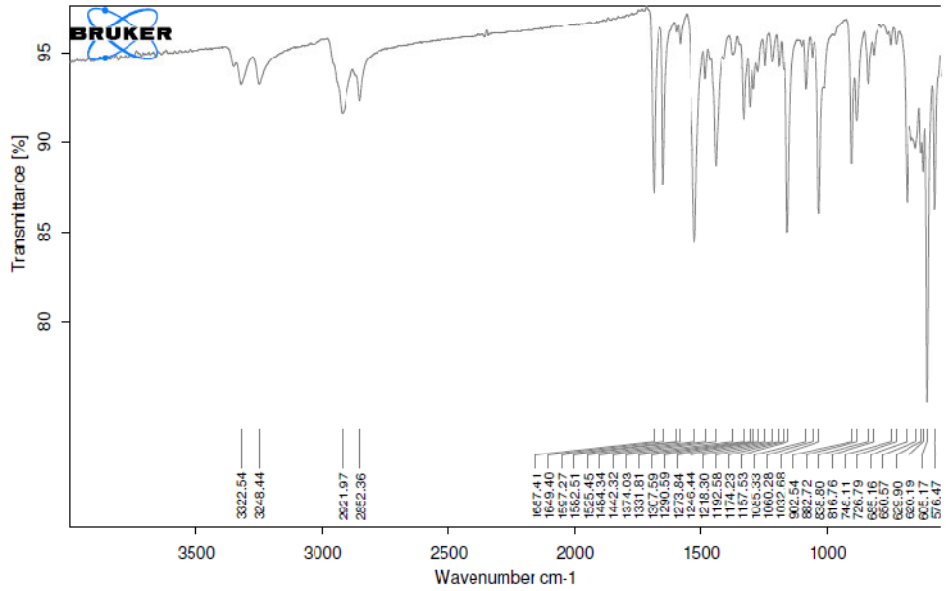

Figure 12: FT-IR Spectrum of Optimised Formulation

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

CONCLUSION

Controlled release tablet of Miglitol tablets were prepared by using Sodium alginate, Carbopol 971P and Ethyl cellulose. Initially chemical interactions were found out using Fourier transform infrared spectrophotometer, from the study it was concluded that there was no chemical interaction between the drug and the excipients used for the formulation of controlled release tablets. The different ratios of drug to polymer were taken for the formulation of different batches. All the nine formulations passed weight variation, friability, hardness, drug content. The dissolution study was done by using USP type II apparatus at 50 rpm/min with 900 ml distilled water (pH 6.8). Only M4 formulation passed the dissolution study for the controlled release tablet and showed better result than the other formulations. On the basis of correlation coefficient value M4 formulation followed Zero order release kinetics model.

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