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Research Article

## Controlled release miglitol microspheres formulation development and evaluation

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Article History	Abstract
Received on: 01-11-2021 Revised on : 14-11-2021 Accepted on : 03-01-2022	The research explain about Miglitol site in the body and also to achieve and maintain the desired ISD concentration, having 2 hour half-life and low bioavailability. The paper give information about nine formulations formulated by using HPMC K15M, Ethyl cellulose and karaya gum in different proportions. The FTIR Spectra revealed that, there was no interaction between polymers and Miglitol. As the polymer ratio was increased, the mean particle size of Miglitol microspheres was also increased. From the results it can be inferred that there was a proper distribution of Miglitol in the microspheres and the deviation was within the acceptable limits. On the basis of release data and graphical analysis formulation F6 containing HPMC K15M showed a good controlled release profile up to 12hrs with maximum entrapment efficiency because of high polymer concentration and follows zero order kinetics with super case II transport mechanism.
<b>Keywords:</b> Miglitol, Ethyl Cellulose, HPMC K15M, FTIR and Karaya gum	
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### Introduction

Floating systems are low - density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a Pro longed period of time. While the system is floating on the gastric contents, the drug is released gradually at the desired rate from the system. After the release of the drug, the remaining system is emptied from the stomach. These outcomes in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, other than a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a low level of floating force F is also required to keep the

dosage form reliably buoyant on the surface of the meal [1]. Floating microspheres are gastro-retentive drug delivery system based on non - effervescent approach and characteristically free flowing powders consisting of proteins or synthetic polymers with diameter s 1µm to 1000µm. As the floating dosage forms provide definite advantages on the bioavailability and controlled the release of drug from the delivery system which is related with the polymer used which is mainly involved in controlling of drug release. Floating dosage forms have been showing high potential for gastro retention and provide an efficient means of enhancing bioavailability and control ling the release of many drugs [2].

Miglitol is chemically called as (2R, 3R, 4R, 5S)-1-(2-hydroxyethyl)-2 (hydroxymethyl) piperidine -3, 4, 5-triol, which inhibits the 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 monosaccharides which can be absorbed by the body.

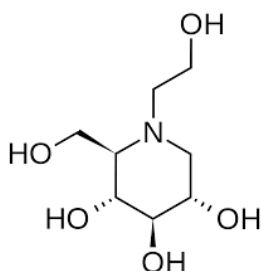


Figure1: Chemical structure of Miglitol

## Experimental work [4-6]

### Materials

Miglitol, API Collected from BMR Chemicals, Hyderabad Karaya gum, Ethyl Cellulose, HPMC K15M, Calcium Chloride, Sodium Alginate all chemicals were Pharma Grade all instruments and equipment alike UV visible spectrophotometer company T60, PG Instrument, FTIR spectrophotometer company Bruker, Magnetic stirrer company Remi Motors, Ahmedabad.

### Methods

#### Preformulation studies [7-8]

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced.

#### Solubility

Solubility of Miglitol was determined in pH 1.2, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Miglitol in different beakers containing different solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions were analyzed spectrophotometrically at 210nm

#### Determination of $\lambda_{max}$

10mg of Miglitol was dissolved in small amount of pH 1.2 acidic buffer then adjust the volume upto 10ml of pH 1.2 buffers so as to get a stock solution of 1000  $\mu\text{g/ml}$  concentration. From the above stock solution pipette out 1ml of the solution and make up the volume to 10ml using buffer to get the concentration of 100  $\mu\text{g/ml}$  concentration.

From this stock solution pipette out 1ml of the solution and make up the volume to 10ml using buffer to get the concentration of 10  $\mu\text{g/ml}$  concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

#### Preparation of standard calibration curve of Miglitol in 0.1N HCL

##### A. Preparation of Stock Solution

10mg of Miglitol was dissolved in small amount of pH 1.2 buffer then volume was up to 10ml with pH 1.2 buffers so as to get a stock solution of 1000  $\mu\text{g/ml}$  concentration

##### B. Preparation Standard Solution

1ml of stock solution was diluted to 10ml with pH 1.2 buffer in 10ml volumetric flask this gives a concentration of 100  $\mu\text{g/ml}$ . Aliquot of standard drug solutions were prepared by withdrawing 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2ml and transferred in to 10ml volumetric flask and were diluted up to the mark with pH 1.2 buffer. This gives the final concentration of 2, 4, 6, 8, 10 and 12  $\mu\text{g/ml}$  of Miglitol respectively. The absorbances of the solution were measured against pH 1.2 as blank using UV visible spectrophotometer. The absorbance values were plotted against concentration ( $\mu\text{g/ml}$ ) to obtain the standard calibration curve.

#### Preparation of Standard Calibration Curve of Miglitol in pH 6.8:

##### A. Preparation of Stock Solution

10mg of Miglitol was dissolved in small amount of pH 6.8 buffer then adjust the volume upto 10ml with pH 6.8 buffer so as to get a stock solution of 1000  $\mu\text{g/ml}$  concentration.

##### B. preparation Standard Solution

1ml of stock solution was diluted to 10ml with pH 6.8 buffer in 10ml volumetric flask this gives a concentration of 100  $\mu\text{g/ml}$ . Aliquot of standard drug solutions were prepared by withdrawing 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2ml and transferred in to 10ml volumetric flask and were diluted up to the mark with pH 6.8 buffer. This gives the final concentration of 2, 4, 6, 8, 10 & 12  $\mu\text{g/ml}$  of Miglitol respectively. The absorbances of the solution were measured against pH 6.8 as blank using UV visible spectrophotometer. The absorbance values were plotted against concentration ( $\mu\text{g/ml}$ ) to obtain the standard calibration curve.

#### Drug polymer interaction (FTIR) study

FTIR spectroscopy was performed on Fourier transformed infrared spectrophotometer (IR-Affinity-1, Shimadzu, Japan). The pellets of drug and potassium bromide were prepared by compressing the powders at

20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000- 600cm<sup>-1</sup>. FTIR study was carried on Miglitol, and polymers, Miglitol loaded microspheres and blank microspheres.

#### Preparation of Miglitol microspheres<sup>7-11</sup>

Microspheres of Miglitol were prepared by ionotropic gelation method using Sodium alginate, Karaya gum, Ethyl Cellulose, HPMC K15M and calcium chloride. Weighed quantity of drug and polymer were added to sodium alginate solution under mechanical stirrer. The resultant solution was then added drop wise to 100 ml of calcium chloride solution under continuous stirring. Stirring was continued for 60minutes. The obtained microspheres were filtered and washed with purified water and then dried for 12 hours at 40°C. Preparation of microspheres was optimized based on entrapment efficiency and release data.

**Table: 1** Formulation design for Miglitol microspheres using different ratios of drug and polymers.

Ingredients (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Miglitol	40 0	40 0	40 0	40 0	40 0	40 0	40 0	40 0	40 0
Sodium Alginate	50 0	50 0	50 0	50 0	50 0	50 0	50 0	50 0	50 0
Karaya gum	20 0	40 0	60 0	-- --	-- --	-- --	-- --	-- --	-- --
Ethyl Cellulose	-- --	-- --	-- --	20 0	40 0	---	-- --	-- --	60 0
HPMC K15M	-- --	-- --	-- --	-- --	-- --	60 0	20 0	40 0	---
Calcium chloride (%)	2	2	2	2	2	2	2	2	2
Distilled water	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S

#### Evaluation of Miglitol Microspheres [7-15]

##### Percentage yield

Percentage practical yield of Miglitol microspheres is calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of Miglitol microspheres recovered

from each batch in relation to the sum of starting material.

The percentage yield of prepared Miglitol microspheres was determined by using the formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

##### Determination of percentage drug entrapment (PDE)

Efficiency of drug entrapment for each batch was calculated in terms of percentage drug entrapment as per the following formula.

$$\text{PDE} = \frac{\text{Practical drug loading}}{\text{theoretical drug loading}} \times 100$$

##### Theoretical drug content

Theoretical drug content was determined by calculation assuming that the entire Miglitol present in the polymer solution used gets entrapped in Miglitol microspheres, and no loss occurs at any stage of preparation of Miglitol microspheres.

##### Practical drug content

**Procedure:** Practical drug content was analyzed by using the following procedure, weighed amount of Miglitol microspheres was dissolved in 100 ml of 6.8pH buffer. This solution was kept overnight for the complete dissolution of the Miglitol microsphere in 6.8pH buffer. This solution was filtered and further diluted to make a conc. of 10 µg/ml solution. The absorbance of the solutions was measured at 210nm using double beam UV-Visible spectrophotometer against 6.8pH buffer solution as blank and calculated for the percentage of drug present in the sample.

##### Surface morphology (SEM)

SEM has been utilized to decide molecule measure dissemination, surface geology, surface, and to look at the morphology of cracked or segmented surface. SEM is most likely for the most part regularly utilized path for describing the measurements sizes and shapes owing in substantial to straightforwardness of test arrangement and simplicity of activity. SEM examines were completed by utilizing JEOL JSM T-330A checking magnifying instrument (Japan). Dry Famotidine gel dot was put on an electron magnifying lens metal stub and covered within a particle sputter. Picture of Famotidine hydrogel globules was taken by arbitrary filtering of the stub.

##### In vitro dissolution studies [16-19]

##### Procedure for Invitro dissolution study

Weight equivalent 25mg Miglitol microspheres were placed in capsule and release rate is determined by employing USP XXIII apparatus by rotating basket

method. The dissolution test was performed using 900 ml 0.1N HCL, in  $37 \pm 0.5^\circ\text{C}$  at 75 RPM for first two hours and the buffer was replaced with 6.8pH phosphate for the remaining time. Miglitol microspheres were filled in capsules and placed in a basket to avoid floating of microspheres. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were passed through whatman filter paper and the absorbance of these solutions was measured at 210nm. Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot. Data obtained was also subjected to kinetic treatment to understand release mechanism.

### Drug Kinetics [20-25]

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order ( $Q$  v/s  $t$ ), first order [ $\text{Log}(Q_0 - Q)$  v/s  $t$ ], Higuchi's square root of time ( $Q$  v/s  $t^{1/2}$ ) and Korsmeyer Peppas double log plot ( $\log Q$  v/s  $\log t$ ) respectively, where  $Q$  is the cumulative percentage of drug released at time  $t$  and  $(Q_0 - Q)$  is the cumulative percentage of drug remaining after time  $t$ . In short, the results obtained from *in vitro* release studies were plotted in four kinetics models are done.

### Results and discussion:

#### Preformulation Studies

#### Solubility study

Miglitol was found to be having more solubility in 6.8 pH buffer when compared to other buffers.

#### Uv Spectrum of Miglitol

The maximum absorbance of the Miglitol in 0.1N HCL was found to be at 210nm.

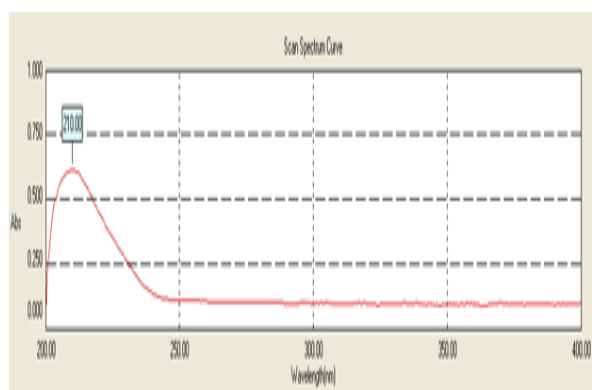


Figure: 2 UV spectra of Miglitol at 210nm

### Standard Calibration Curve

#### Standard calibration data of Miglitol in 0.1N HCL

Table: 2 Standard calibration data of Miglitol in 0.1N HCL

Concentration ( $\mu\text{g/ml}$ )	Absorbance
0	0
2	0.126
4	0.248
6	0.342
8	0.482
10	0.593
12	0.716

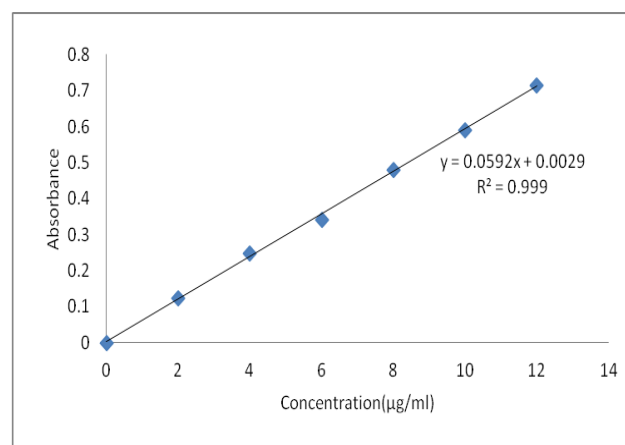
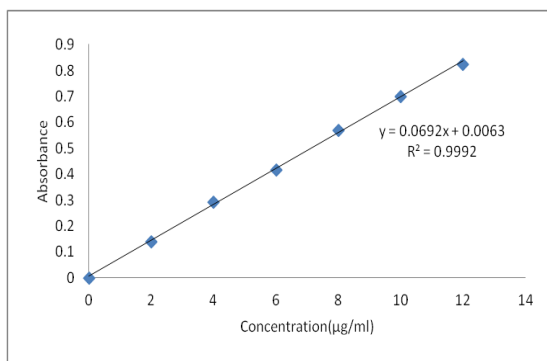


Fig: 3 Calibration curve of Miglitol in 0.1N HCL

#### Standard calibration data of Miglitol in 6.8pH buffer

Table: 3 Standard calibration data of Miglitol in 6.8pH buffer

Concentration ( $\mu\text{g/ml}$ )	Absorbance
0	0
2	0.141
4	0.293
6	0.418
8	0.571
10	0.702
12	0.825



**Evaluation of Miglitol Microspheres**

**Drug polymer interaction (FTIR) study**

From the drug excipient compatibility studies we observed that there are no interactions between the pure drug (Miglitol) and optimized formulation (Miglitol+excipients) which indicates there are no physical changes.

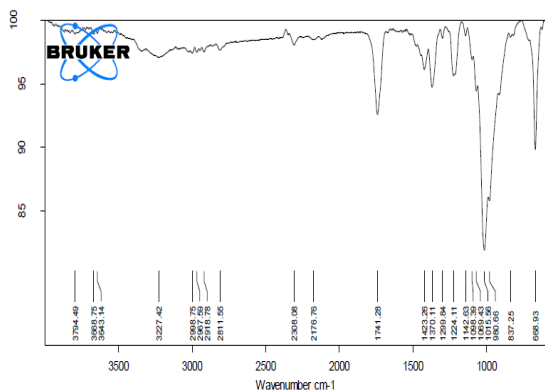


Figure: 5 IR spectra of Pure Miglitol:

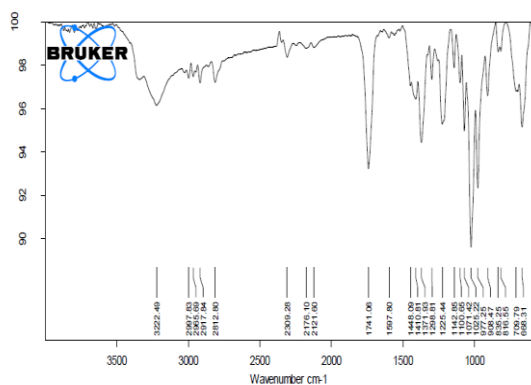


Figure: 6 IR spectra of Miglitol and Excipients

Table 4: Percentage yield

Formulation Code	Percentage Yield (%)
F1	62.41
F2	73.28
F3	83.16
F4	61.86
F5	79.32

F6	86.13
F7	82.63
F8	84.16
F9	87.36

Table 5: Determination of Percentage Entrapment efficiency

Formulation Code	Entrapment Efficiency (%)
F1	92.16
F2	95.43
F3	98.32
F4	95.72
F5	99.23
F6	95.36
F7	97.18
F8	95.43
F9	96.75

**Surface morphology scanning Electron Microscopy (SEM)**

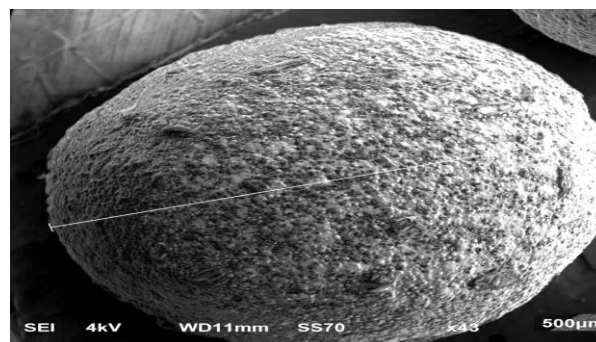


Figure: 6 SEM analysis of optimized formulation of Miglitol

**In Vitro Dissolution Studies**

Table: 6 in Vitro Release Data of Miglitol Microspheres

Time (hrs)	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	36.18	32.16	28.43	31.06	26.31	8.73	22.18	15.43	20.16
2	52.63	41.86	36.42	39.15	36.18	19.26	29.53	23.42	32.16
3	61.89	51.36	42.18	46.31	46.13	27.84	36.41	29.86	39.46
4	69.42	59.73	53.85	52.36	49.75	36.43	42.19	32.15	45.12
5	76.42	65.42	64.42	59.42	53.42	44.42	49.42	46.42	53.42

	08	07	53	76	46	81	83	18	18
6	89. 63	72. 41	72. 19	65. 52	62. 15	55. 32	58. 32	52. 76	64. 86
7	99. 43	86. 43	79. 53	72. 43	69. 63	64. 13	64. 17	63. 8	71. 52
8		95. 08	86. 41	86. 49	75. 14	70. 85	76. 92	72. 63	79. 63
9			91. 05	98. 62	89. 36	79. 26	86. 32	81. 69	83. 42
10			96. 43		96. 43	86. 59	91. 74	86. 75	92. 43
11						92. 43	98. 72	92. 16	97. 05
12						97. 26			

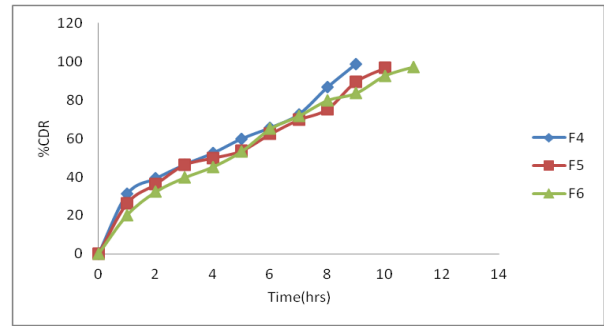


Figure:9 % CDR profile of Miglitol microspheres F4-F6

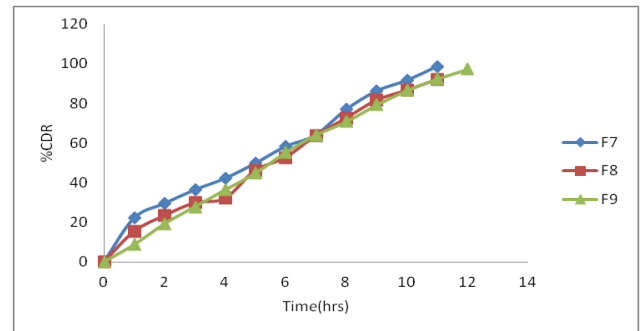


Figure: 10 % CDR profile of Miglitol microspheres F7-F9

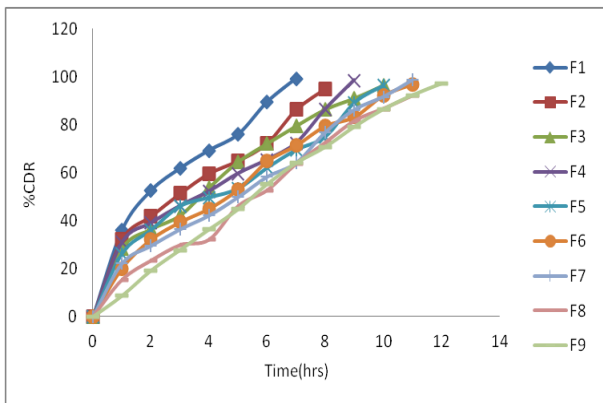


Figure: 7 % CDR profile of Miglitol microspheres F1-F9

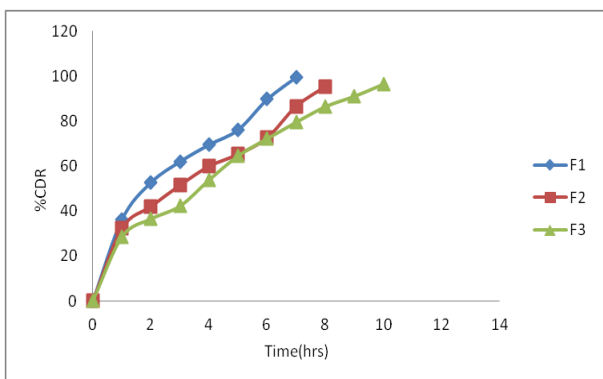


Figure:8 % CDR profile of Miglitol microspheres F1-F3

**Drug Release Kinetics Studies:**

**Zero Order Release:**

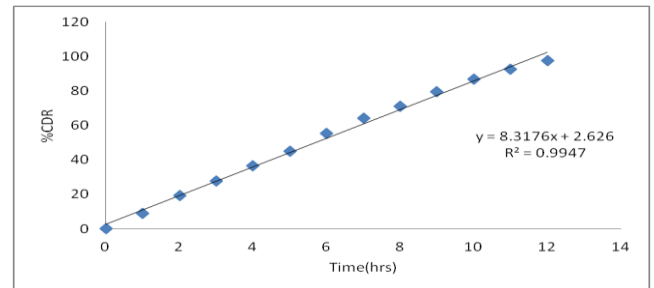


Figure: 11 Zero order release profile of F6

**First Order Release:**

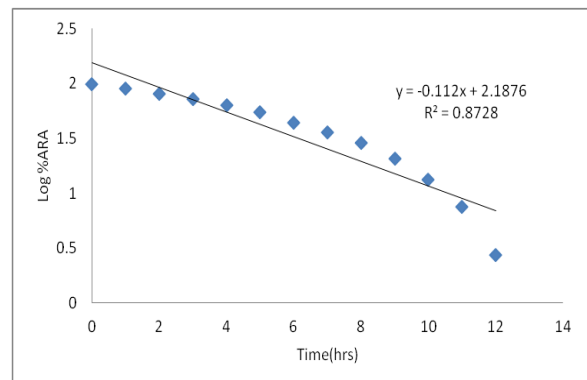
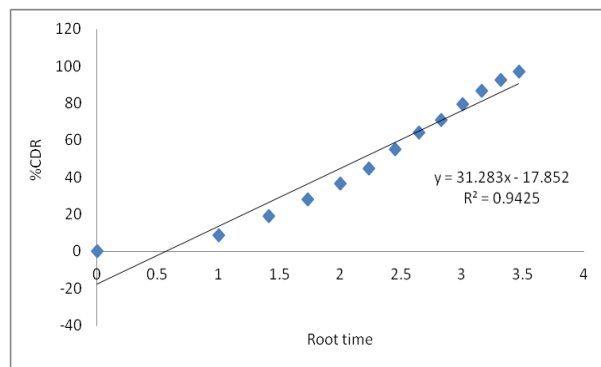
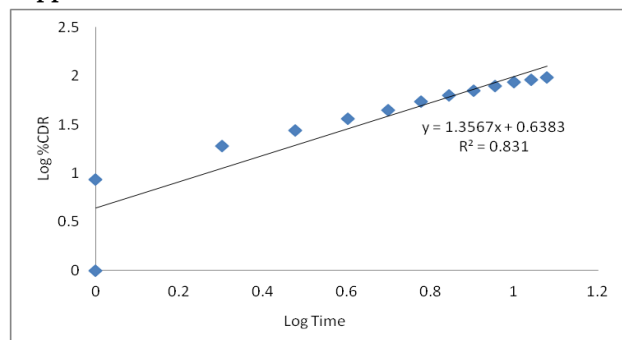


Figure:12 First order release profile of F6

**HIGUCHI RELEASE PLOT:****Figure: 13 Higuchi release kinetics profile of F6****Pappas Release Plot:****Figure: 14 Peppas release kinetics profile of F6****Table: 7 Regression co-efficient ( $r^2$ ) values Miglitol microspheres**

Formula-	Zero	First	Higuchi Ma-		
				$r^2$	'n' value
F6	0.9	0.8	0.94	0.8	1.3

From the drug release kinetics it was observed that the optimized formulation (F9) follows zero order drug release with super case II transport mechanism, as the n value was  $>0.89$ .

**DISCUSSION**

In the present work, total nine formulations were prepared and the detailed composition is shown in Table. The prepared Miglitol microspheres were then subjected to FTIR, % yield, entrapment efficiency, *in vitro* dissolution, and scanning electron microscopy. FTIR Spectra were obtained for Miglitol and polymer microspheres, of Karaya gum, HPMC K15M, & Ethyl cellulose, the characteristic peaks of the Miglitol were compared with the peaks obtained for drug and polymers. The percentage yield for Miglitol microspheres were in the range of 62.41 to 87.36 %. Entrapment effi-

ciency increases with increase in the polymer concentration. From the results it can be inferred that there is a proper distribution of Miglitol in the microspheres and the deviation is within the acceptable limits.

The percentage entrapment efficiency was found to be 92.16 % to 99.23 %. Total 9 formulations of Miglitol microspheres are designed using polymers (HPMC K15M, Ethyl cellulose & Karaya gum) with different ratio. F1-F3 formulations are formulated using Drug: karaya gum with different ratios. F1 formulations containing Drug: karaya gum in the ratio of 1:0.5 shows maximum drug release at the end of 7<sup>th</sup> hour. F2 formulations containing Drug: karaya gum in the ratio of 1:1 shows maximum drug release at the end of 8<sup>th</sup> hour. F3 formulations containing Drug: karaya gum in the ratio of 1:1.5 shows maximum drug release at the end of 10<sup>th</sup> hour. Above formulations couldn't showed sustained drug release upto 12hrs. So further trails were formulated using Ethyl cellulose with same ratios. F4-F6 formulations are formulated using Drug: Ethyl cellulose with different ratios. F4 formulations containing Drug: Ethyl cellulose in the ratio of 1:0.5 shows maximum drug release at the end of 9<sup>th</sup> hour. F5 formulations containing Drug: Ethyl cellulose in the ratio of 1:1 shows maximum drug release at the end of 10<sup>th</sup> hour. F6 formulations containing Drug: Ethyl cellulose in the ratio of 1:1.5 shows maximum drug release at the end of 11<sup>th</sup> hour. Above formulations couldn't showed sustained drug release upto 12hrs. So further trails were formulated using HPMC K15M with same ratios. F7-F9 formulations are formulated using Drug : HPMC K15M with different ratios. F7 formulations containing Drug : HPMC K15M in the ratio of 1:0.5 shows maximum drug release at the end of 10<sup>th</sup> hour. F8 formulations containing Drug : HPMC K15M in the ratio of 1:1 shows maximum drug release at the end of 11<sup>th</sup> hour. F9 formulations containing Drug : HPMC K15M in the ratio of 1:1.5 shows maximum drug release at the end of 12<sup>th</sup> hour. The *in vitro* performance of Miglitol Microspheres showed prolonged and controlled release of Miglitol. The results of the *in vitro* dissolution studies showed controlled release in a predictable manner. As the polymer concentration was increased, the drug release from the Microspheres were found to decrease. Compared to karaya gum and ethyl cellulose, HPMC K15M retarded drug release more effectively, microspheres had an optimum release at the end of 12<sup>th</sup> hour. Based upon our aim and Objective the main aim was to controlled the drug delivery by Microspheres, the maximum drug was controlled in HPMC K15M

formulations than the other polymers. The plots of cumulative percentage drug release V/s. time, cumulative percent drug retained V/s. root time, log cumulative percent drug retained V/s. time and log cumulative percent drug release V/s. log time were drawn and represented graphically as shown in Figure and table respectively. The slopes and the regression co-efficient of determinations ( $r^2$ ) were listed in Table. The co-efficient of determination indicated that the release data was best fitted with zero order kinetics. Higuchi equation explains the diffusion controlled release mechanism. The diffusion exponent 'n' values of Korsmeyer-Peppas model was found to be in the range of 1.35 for the Miglitol microspheres prepared with drug and HPMC K15M indicating super case II transport mechanism of drug through Miglitol microspheres.

### Conclusion

An attempt was made to prepare microspheres of Miglitol ionic gelation techniques by using polymers like Karaya gum, HPMC K15M, and Ethyl cellulose achieve an oral controlled release of the Miglitol. In the present study nine formulations were formulated by using Karaya gum, HPMC K15M, and Ethyl cellulose in various concentrations. On the basis of release data and graphical analysis formulation F6 showed a good controlled release profile with maximum entrapment efficiency because of high polymer concentration. The co-efficient of determination indicated that the release data was best fitted with zero order kinetics. The diffusion exponent 'n' values of Korsmeyer-Peppas model was found to be in the range of 1.35 for the Miglitol microspheres prepared with drug and HPMC K15M indicating super case II transport mechanism of drug through Miglitol microspheres.

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