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Design and Development of Miglitol Loaded PLGA Polymeric Naoparticles

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Abstract: In the present study, Miglitol loaded PLGA Polymeric naoparticles (MNP1-MNP10) were prepared for the controlled release of Miglitol using different concentrations of PLGA. The prepared nanoparticles also coated with Eudragit S100 for intestinal targeting of Miglitol. Miglitol loaded PLGA Polymeric naoparticles (MNP1-MNP10) Nanoparticles were characterized for various physical parameters such as particle size, zeta potential and particle size distribution and chemical parameters such as drug content, entrapment efficiency and *In vitro* drug release studies. The prepared Miglitol loaded PLGA Polymeric nanoparticles with 120 mg of PLGA have shown average particle size 200.2±0.32nm, average zeta potential of -18.4±0.43mV, average entrapment efficiency 90.46±0.81%, average drug content of 98.88±0.62 % and average i*n vitro* drug release 98.16±0.19 % at the end of 24 hrs. DSC and FTIR study concluded that no interaction occurred between the Miglitol and other polymers used in the present study.
Key words: PLGA, Eudragit S 100,Zeta potential, entrapment efficiency.

Introduction

Miglitol is a drug commonly used in the management of Type 2 diabetes mellitus which belongs to the category of alpha-glucosidase enzyme inhibitor. Miglitol delay the absorption of carbohydrates from the gastrointestinal tract, thereby limiting postmeal plasma glucose excursions[1].

Miglitol is well absorbed from GIT. Hence the delivery of Miglitol in oral route helps to improve absorption and improve the efficacy. In view of the limitations of the conventional oral Miglitol tablets, which are required to be administered at different time intervals leading to inconvenience to the patients, demands the development of Nanoparticulate drug delivery of Miglitol[2,3]. Administration of Miglitol in nanoparticulate drug delivery system will help to release the drug in continuously for 24 hrs which improves the patient compliance as well as therapeutic efficacy.

These systems have been investigated primarily for controlled drug delivery of Miglitol, and also for the enhancement of dissolution rate/bioavailability of Miglitol.

So the aim of the present study was to formulate Miglitol loaded PLGA nanoparticles for the controlled release of drug so that its frequency of administration can be avoides and its bioavailability can be enhanced[4,5].

Materials and Methods

Miglitol was obtained as gift sample from Micro labs Pvt.ltd, Bangalore. PLGA and Pluronic F68 were purchased from Sigma Aldrich. Dichloromethane was purchased from Loba chemie pvt.ltd, Chennai. The other

chemicals used in the preparation and evaluation are of analytical grade

Formulation of Miglitol Loaded PLGA Polymeric Naoparticles[6,7,8]

Preformulation Studies

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It is defined as an investigation of physical and chemical properties of a drug substance. The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms.

Drug-Excipient Compatibility Studies

Each excipient used in the formulations was blended thoroughly with Miglitol to increase drug-excipient molecular contacts to accelerate the reactions if possible. Each drug- excipient blend was taken separately into the vials and kept for a month and two months study at 40ºC. After, that each blend was tested for stability by physical observation and assay.

Fourier Transform infra Red spectroscopy

TIR spectroscopy was used to ensure that no chemical interaction between Miglitol and the other excipients used in the formulation. IR spectra of Miglitol and other excipients used in the formulation were recorded by using"Perkin-elmer FTIR." The sample for the IR spectroscopy was prepared by mixing the samples with spectroscopic grade KBr and compressed in to transparent pellets, then scanned in the IR range from 500 to 4000 cm^{-1} with a resolution of 4 cm.

Differential Scanning calorimetry(DSC technique)

Differential Scanning Calorimetry studies for Miglitol, excipients and combinations of Miglitol with excipients were carried out using "Schimadzu DSC-60. In this study Miglitol was mixed with the excipients used in the formulation and thermal analysis of each sample was carried out. During the study, the temperature ranges from 25 to 400º C, heating rate 10ºC/min and flow rate of nitrogen 30 ml/min were maintained. The samples approximately 5 mg were taken in aluminium pan, sealed and recorded the thermogram.

Miglitol loaded PLGA nanoparticles by double emulsification solvent- evaporation[6,7]

Miglitol (50mg) was dissolved in 10ml water and added to 60ml of Dichloromethane containing PLGA and the solution was emulsified under high shear homogenizer (10000 rpm) to form primary w/o nano emulsion which was subsequently transferred into the aqueous phase containing (1%v/w) Pluronic F- 68. The mixture was emulsified under high shear homogenizer at 24000 rpm to form w/o/w nano emulsion. The nano emulsion was stirred overnight at room temperature in order to evaporate the organic solvent. The resulting nanoparticles suspension was separated by high speed centrifugation (13000 for 1 hour) and the sediment was dried using 2% D-mannitol as a cryoprotectant.

Table 1. Formula used for the preparation of Miglitol loaded PLGA nanoparticles

S.No	Formulation	Drug (mg)	Polymer PLGA(mg)	Pluronic F-68 (%)	Dichloro methane (ml)
1.	MNP1	50	50	1	60
2.	MNP2	50	60	1	60
3.	MNP3	50	70	1	60
4.	MNP4	50	80	1	60
5.	MNP5	50	90	1	60
6.	MNP6	50	100	1	60
7.	MNP7	50	110	1	60
8.	MNP8	50	120	1	60
9.	MNP9	50	130	1	60
10.	MNP10	50	140	1	60

Coating of Miglitol loaded PLGA nanoparticles[7]

The coating of Miglitol loaded PLGA nanoparticles were prepared by a simple solvent evaporation method. The enteric coating solution was composed of 12% Eudragit S100 in acetone. Coating was obtained by dispersing 100 mg of Miglitol loaded PLGA nanoparticles in coating solution with a core: coat ratio of 1:10 followed by solvent evaporation in a rotary evaporator. Samples of coated Miglitol loaded PLGA nanoparticles were then dried and weighed

Evaluation[8,9,10]

Particle size and zeta potential

The prepared nanoparticles were evaluated for their particle size and zeta potential by photon correlation spectroscopy (PCS) using Zetasizer.[10]The formulations were diluted to 1:1000 with the aqueous phase of the formulation to get a suitable kilo counts per second (kcps). Analysis was carried out at 25°C with an angle of detection of 90°.

Drug content

Stabdard preparation:

Weighed accurately 25mg of Miglitol and transferred in to a 25 ml standard flask. The sample was dissolved with 5 ml of pH 6.8 phosphate buffer and diluted to 25 ml with buffer. 1ml of this solution was diluted to 25ml with buffer solution.

Sample preparation :

Weighed accurately 1gm of Miglitol nanoparticles and transferred in to a 25 ml standard flask. The sample was dissolved with 5 ml of pH 6.8 phosphate buffer and diluted to 25 ml with pH 6.8 phosphate buffer. 1ml of this solution was diluted to 25ml with buffer solution.

Then the standard and sample absorbance were measured at 232 nm using a UV-Visible spectrophotometer. From the absorbance values the percentage of drug content was calculated.

Entrapment efficiency

Separation of unentrapped Miglitol from the prepared Miglitol nanoparticles were carried out by centrifugation method. Miglitol nanoparticles formulations were centrifuged at 15000 rpm for 30min. The supernatant solution was separated. 1ml of this supernatant was diluted with water and the absorbance was measured at 232 nm using water as blank. The amount of Miglitol unentrapped in the supernatant was calculated. The amount of Miglitol entrapped was determined by subtracting amount of free unentrapped Miglitol from total amount of Miglitol taken for the preparation.

The formula used to calculate encapsulation efficiency was given below

$$\text{Encapsulation efficiency} = \frac{\text{Entrapped drug (mg)}}{\text{Total amount of drug added (mg)}} \times 100$$

***In vitro* drug release studies**

In vitro release studies were performed using dialysis membrane method. The prepared Miglitol nanoparticles formulation was placed inside a dialysis membrane immersed in pH 6.8 phosphate buffer. At predetermined time intervals the sample was withdrawn and the amount of Miglitol released was determined by measuring the absorbance at 232 nm using a UV-Visible spectrophotometer. From the absorbance values the cumulative percentage drug release was calculated[2,3].

Results and Discussion

Preformulation Studies

Compatibility study using IR and DSC

- In the IR spectrum of Miglitol standard consists of characteristics band values at 3811 cm^{-1}(C-H-bending), 2816 cm^{-1}(C-H-stretching) and 1597cm^{-1} (N-H-stretching). These characteristic band values were observed in all the recorded IR spectra.
- DSC of Miglitol showed a sharp endothermic peak at 147.02^{0}C (melting point). The physical mixture of Miglitol and other excipients also showed the same thermal behavior as the individual component.
- DSC results also revealed that the physical mixture of Miglitol with excipients showed superimposition of the thermograms. There was no significant change observed in melting endotherm of physical mixture of Miglitol and excipients.
- From the IR and DSC studies, it was found that there were no interaction took place between Miglitol and the other ingredients used in the formulation of Miglitol nanoparticles. The IR spectra and DSC images were shown from **Fig.1 to Fig. 4.**

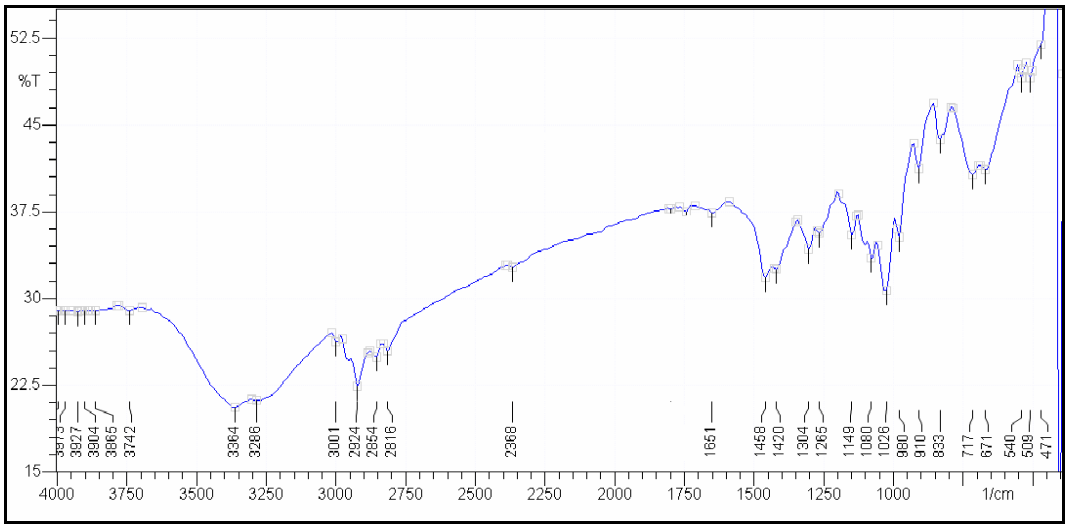


Fig.1. IR spectrum of miglitol standard

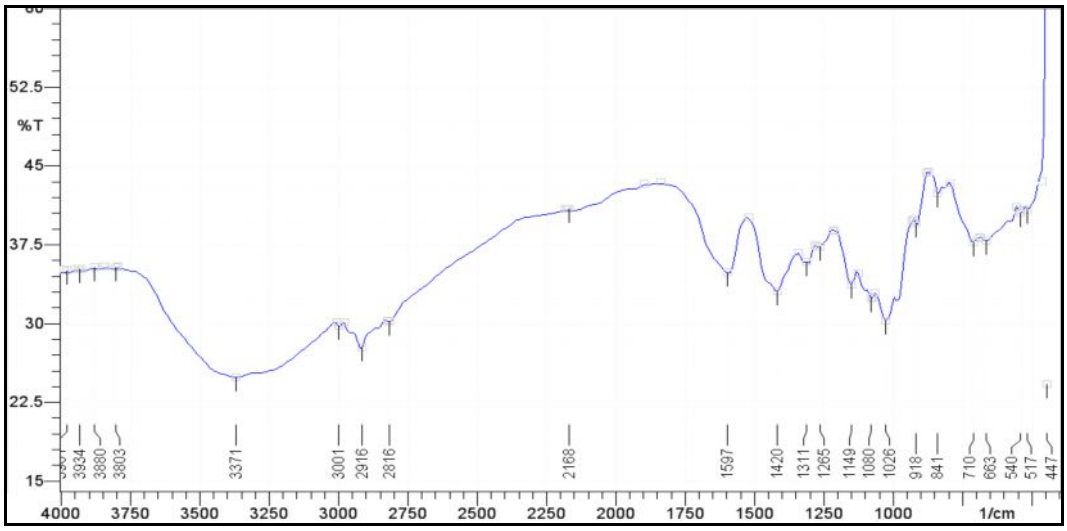


Fig.2.IR spectrum of blend of Miglitol nanoparticles

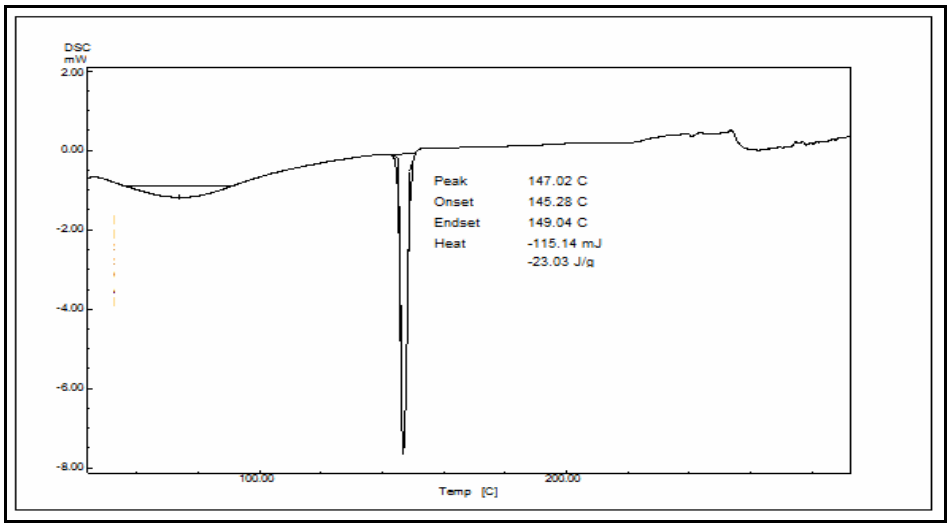


Fig.3.DSC of Miglitol

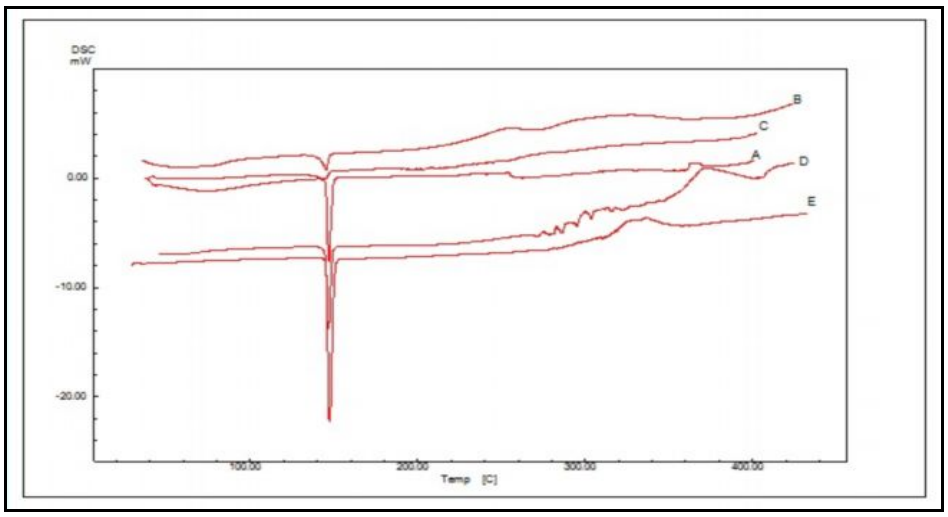


Fig.4.DSC thermograms of A.Miglitol STD,B. Miglitol sample, C.Miglitol+Pluronic, D.Miglitol+PLGA,E. Miglitol NP

Particle Size , Zeta Potential and Entrapment Efficiency

Table 2. Zeta potential, Particle size and Entrapment efficiency of MNP1-MNP10

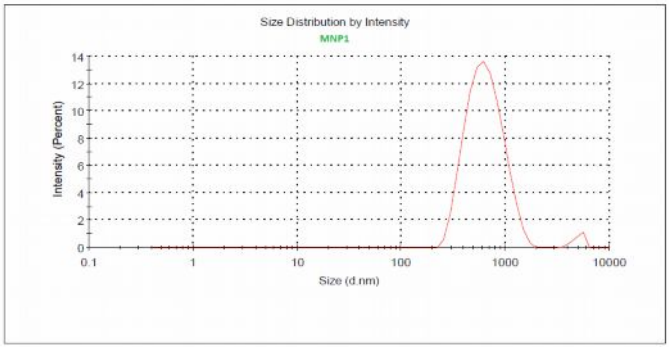
Trials	Particle size(nm)	Zeta potential (mV)	Entrapment Efficiency (%)	Drug content (%)
MNP1	157.4±0.12	-28.3±0.14	35.72±0.23	98.45±0.43
MNP2	167.1±0.34	-24.5±0.26	40.67±0.45	97.56±0.19
MNP3	173.4±0.56	-22.8±0.57	45.89±0.65	98.12±0.72
MNP4	177.4±0.66	-21.6±0.52	53.62±0.28	97.78±0.28
MNP5	180.1±0.45	-20.9±0.14	62.15±0.22	97.39±0.61
MNP6	185.5±0.73	-19.6±0.46	70.84±0.16	98.24±0.54
MNP7	196.7±0.25	-18.7±0.27	85.16±0.42	97.86±0.67
MNP8	200.2±0.32	-18.4±0.43	90.46±0.81	98.88±0.62
MNP9	272.7±0.53	-17.3±0.68	90.52±0.67	97.39±0.17
MNP10	300.4±0.46	-15.4±0.28	90.55±0.56	97.72±0.34

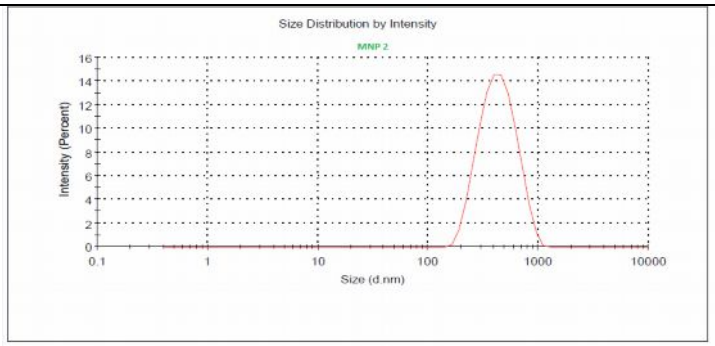
mean±S.D, n=3

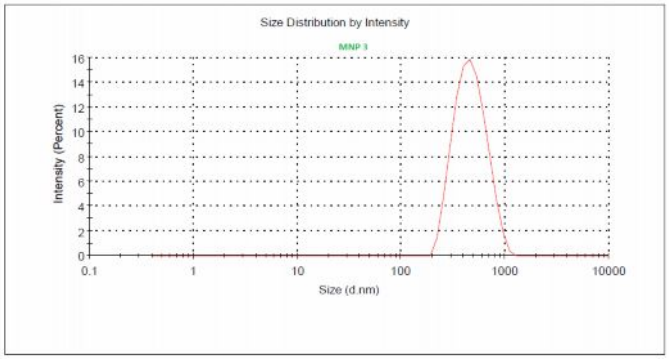
- The mean particle size of Miglitol loaded PLGA nanoparticles is shown in Table 2. The average particle sizes of the formulations were range from 157.4±0.12 nm to 300.4±0.46 nm (MNP1-MNP10) respectively.

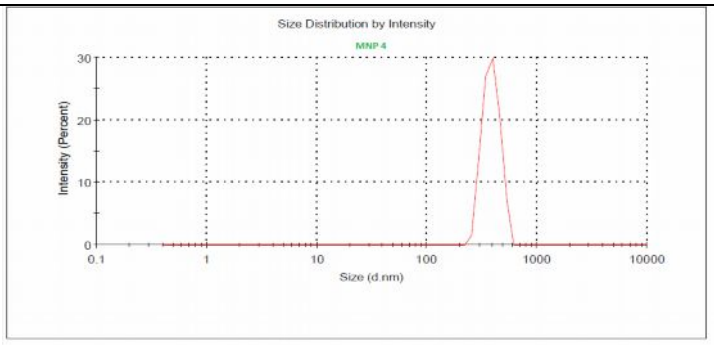
- The particle size dependant on PLGA concentration. The smallest particle size of the developed formulation was found in trial MNP1 (157.4±0.12 nm) and largest particle size was found in trial MNP10 (300.4±0.46 nm). The results suggested that in an increase in PLGA concentration increase the particle size.
- Particle size and entrapment efficiency of the Miglitol Nanoparticles (MNP1-MNP8) were increased with increasing the PLGA concentration. This may be due to high amount of availability of PLGA to encapsulate the drug, upon increasing the PLGA concentration, number of layers of coated drug was increased, and this resulted in increased particle size and entrapment efficiency[10,11].
- Further increase in the PLGA concentration to 140 mg as in (MNP9 and MNP10), there is no much increase in the entrapment efficiency due to the availability of the drug to be incorporated is low which is not enough for further encapsulation of drug by PLGA.

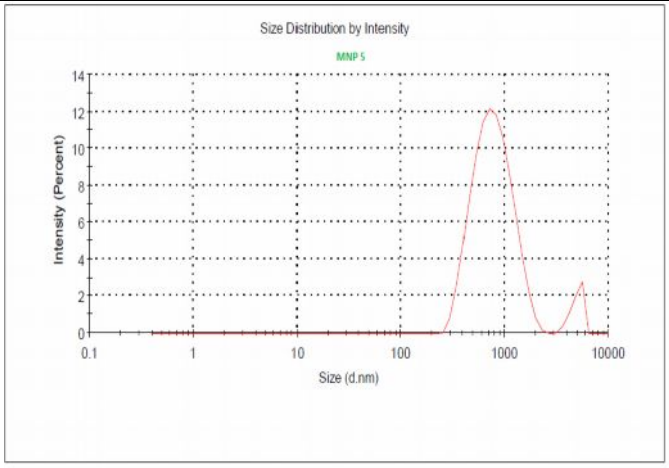
There was no significant changes in the drug content of all the formulations.The results of particle size and zeta potential were given in fig.5 to fig.14.

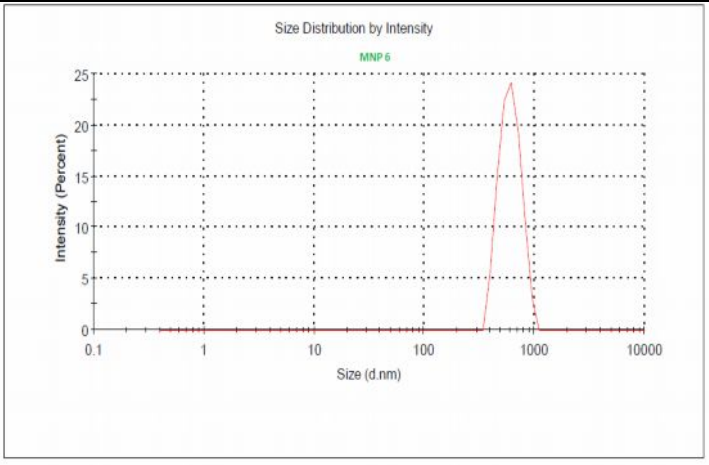












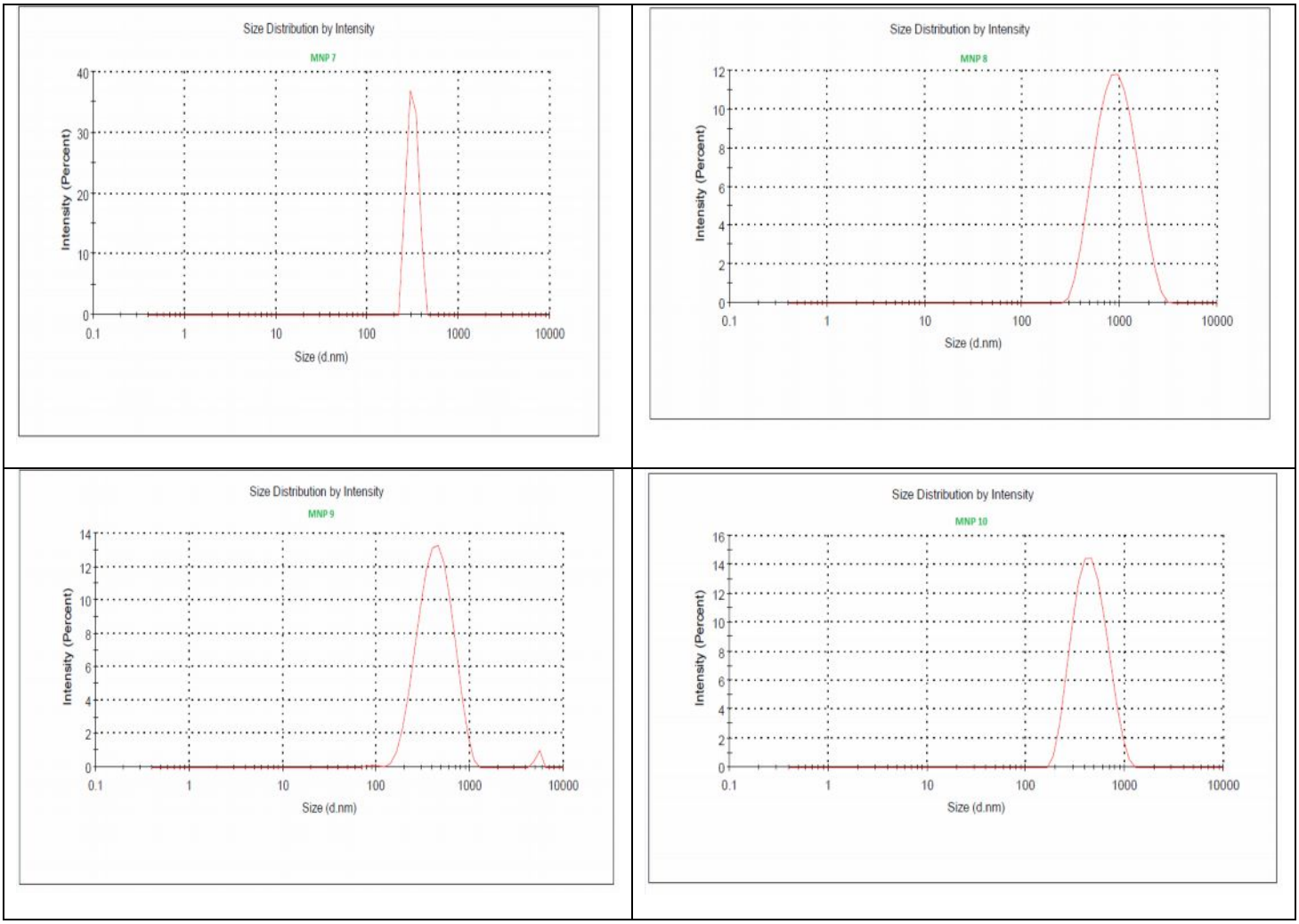


Fig.5-14 Particle size of Miglitol nanoparticles (MNP5-MNP14)

In vitro drug release studies

Table 3. Percentage *In vitro* drug release of MNP1-MNP5

Trials/ Time (h)	MNP1	MNP2	MNP3	MNP4	MNP5
0.5	14.54±0.17	13.57±0.33	12.36±0.45	10.56±0.14	8.89±0.34
1	24.67±0.24	22.65±0.23	20.24±0.17	18.76±0.37	16.56±0.66
1.5	35.35±0.35	33.57±0.12	30.76±0.28	28.67±0.45	26.83±0.19
2	47.34±0.46	45.78±0.27	40.48±0.44	38.95±0.56	36.78±0.36
2.5	59.78±0.23	58.42±0.86	51.47±0.72	49.78±0.72	46.78±0.42
3	70.76±0.15	69.28±0.34	61.38±0.45	58.39±0.28	56.35±0.78
4	83.65±0.31	81.39±0.24	76.37±0.18	73.27±0.82	70.36±0.83
6	92.87±0.12	90.48±0.21	82.86±0.63	80.26±0.65	78.62±0.37
8	97.86±0.22	97.84±0.58	90.56±0.28	87.49±0.43	84.39±0.49
10	97.88±0.18	97.85±0.39	97.74±0.82	97.83±0.18	93.67±0.26
12	-	-	97.81±0.54	97.83±0.07	97.69±0.58
16	-	-	-	-	97.81±0.92
20	-	-	-	-	-
24	-	-	-	-	-

Table 4. Percentage *In vitro* drug release of MNP6-MNP10

Trials/Time(h)	MNP6	MNP7	MNP8	MNP9	MNP10
0.5	7.92±0.12	7.24±0.26	5.58±0.14	4.76±0.42	3.82±0.27
1	15.73±0.24	14.45±0.16	11.75±0.25	9.64±0.25	8.37±0.68
1.5	25.35±0.13	24.46±0.34	16.94±0.27	15.38±0.35	12.68±0.16
2	34.96±0.33	33.67±0.45	23.42±0.18	21.45±0.47	19.76±0.27
2.5	44.65±0.36	43.56±0.41	28.82±0.41	25.64±0.48	21.58±0.38
3	55.39±0.54	50.46±0.48	33.85±0.58	31.37±0.15	29.36±0.75
4	68.87±0.18	65.62±0.83	47.14±0.47	43.38±0.49	40.47±0.28
6	77.45±0.45	75.35±0.91	66.47±0.18	63.24±0.51	59.44±0.42
8	82.86±0.65	79.56±0.18	70.18±0.39	66.26±0.33	61.24±0.74
10	90.62±0.34	87.42±0.34	75.09±0.65	70.26±0.61	68.35±0.28
12	93.05±0.16	90.63±0.31	80.35±0.26	74.39±0.75	71.67±0.44
16	98.01±0.47	94.53±0.08	87.43±0.17	79.58±0.34	77.62±0.08
20	-	97.86±0.35	93.45±0.24	85.55±0.08	82.61±0.43
24	-	-	98.16±0.19	91.84±0.63	88.72±0.36

- The *in vitro* drug release rate of all the trials (MNP1-MNP10) were decreased with increasing the PLGA concentrations.
- The smaller size Miglitol nanoparticles prepared with lower concentration of PLGA exhibited immediate drug release rate (97.86±0.22,MNP1), this is may be due to the increased nanoparticle surface resulting in larger drug fraction exposed to the dissolution medium.
- For all the seven batches (MNP1-MNP7), about Maximum percentage of drug was released within 20 hours . On the other hand, the increase in PLGA concentrations prolonged the Miglitol release from nanoparticles.
- The *invitro* drug release of MNP1-MNP7 were found to be released within a short duration which is not desirable as the concentration of PLGA (50-110mg) was not sufficient to extend the drug release up to 24hrs.
- From the *in vitro* drug release studies results of the Miglitol nanoparticles (MNP1-MNP10), the maximum percentage drug release (98.16±0.19) at the end of 24h was observed with trial MNP8 which contains 120mg of PLGA.
- Further increase in the PLGA concentration from 130 mg to 140 mg as in (MNP9and MNP10), prolonged the Miglitol release from nanoparticles .The maximum percentage drug release at the end of 24 hrs was found to be 91.84±0.63 and 88.72±0.36 for MNP 9 and MNP 10 respectively.
- From the *in vitro* drug release data for MNP1-MNP10, it was observed that the concentration of PLGA plays a major role in the *in vitro* drug release profile of prepared Miglitol nanoparticles[11-16].
- From all the trials MNP8 was selected as optimized formulation for further performance evaluation study, comparative study and stability study because of its ideal particle size, high entrapment efficiency, the desirable and maximum drug release.

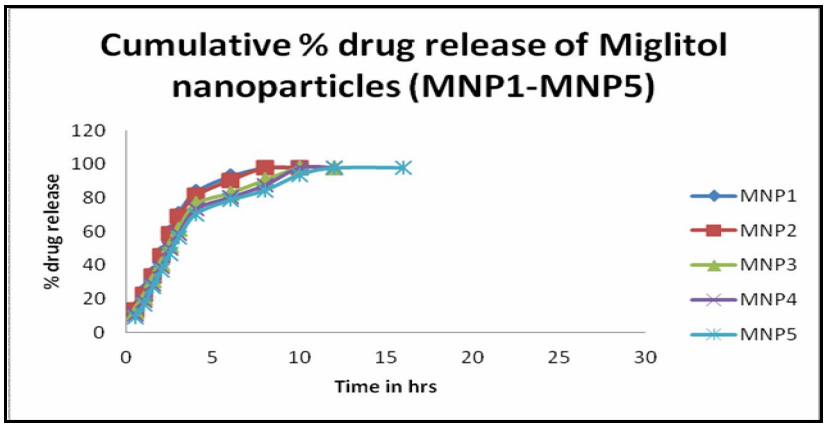


Fig.15. Miglitol nanoparticles (MNP1-MNP5)

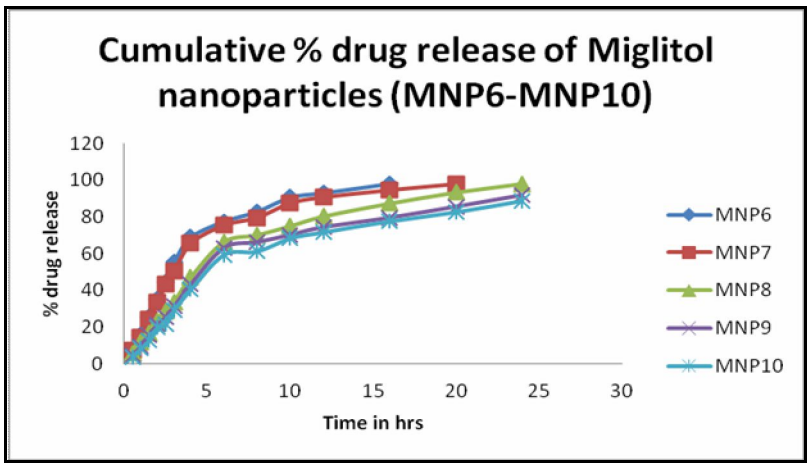


Fig.16. Miglitol nanoparticles (MNP6-MNP10)

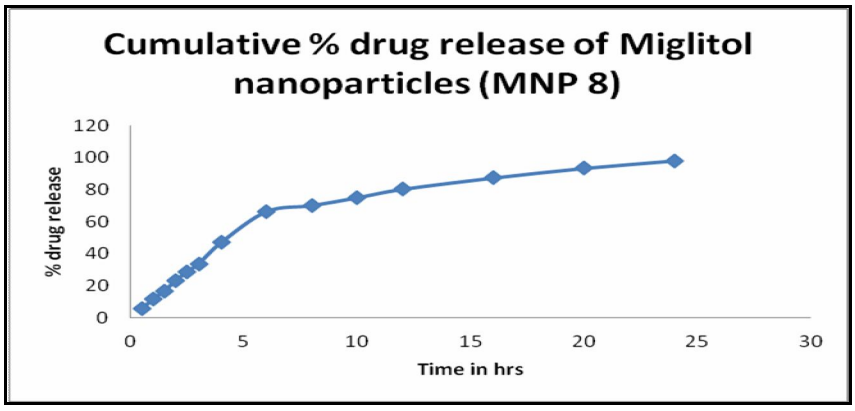


Fig.17. Miglitol nanoparticles (MNP 8)

Summary and Conclusion

The prepared dosage forms were optimized and evaluated *in vitro* and *in vivo*. The preformulation studies were carried out for the drug and excipients to develop the final formulation. Drug excipient compatibility studies suggested that there was no interaction between Miglitol and other excipients used in the formulation of Miglitol nanoparticles.

Miglitol nanoparticles were formulated using PLGA as polymer in different concentrations. The results of the *in vitro* release studies showed that the formulation MNP 8 was found to ideal for controlled release. The maximum *in vitro* drug release of 98.16±0.19 % was obtained for the Miglitol nanoparticles prepared with 120 mg of PLGA. The optimized formulation of Miglitol nanoparticles (MNP8) was subjected to stability studies as per ICH guidelines. No significant changes in the physical and chemical characteristics were observed during the stability studies of Miglitol nanoparticles (MNP8).

Conclusion

The present study was made to develop the nanoparticulate drug delivery of Miglitol. Miglitol nanoparticles were formulated and evaluated. Miglitol nanoparticles were prepared with different concentrations of PLGA were optimized by conducting various trials. The optimization procedure aided in the preparation of Miglitol nanoparticles with controlled drug release up to 24 hrs. The *in vitro* dissolution studies revealed that the formulated Miglitol nanoparticles released the desired concentration of the drug continuously for 24 hrs. The stability studies on the selected formulation of Miglitol nanoparticles were found to be stable. Hence it may be concluded that the newly formulated nanoparticulate drug delivery systems of Miglitol produce effective control of the increased blood glucose level after intake of meals by allowing the drug to release continuously up to 24 hrs

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