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Preformulation Parameters Characterization to Design, Development and Formulation of Miglitol Loaded Nanoparticles

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Abstract:

The purpose of the present study was to systematically investigate some of the important physicochemical properties of Miglitol loaded nanoparticle. Miglitol is an oral medication used to control blood glucose (sugar) levels in type 2 diabetes. It belongs to a class of drugs called alpha-glucosidase inhibitors which also includes acarbose. Carbohydrates that are eaten are digested by enzymes in the intestine into smaller sugars which are absorbed into the body and raise blood sugar levels. Almost all drugs are marketed as tablets, capsules or both. Prior to the development of these major dosage forms, it is essential that pertain fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder are determined. This information decides many of the subsequent events and approaches in formation development. A modified release nanoparticle of Miglitol was prepared by solvent evaporation method using Poly (lactic-co-glycolic acid) PLGA as coating material. So before selection of excipients, the Preformulation study of drug Miglitol is completed for successful formulation of modified release nanoparticle. Preformulation studies included solubility, pKa, dissolution, melting point, assay development, stability in Solution, stability in solid state; microscopy, bulk density, flow properties, excipient compatibility, entrapment efficiency and release profile of nanoparticles were investigated. The experimental values and results of this study will be presented.

Key words: *nanoparticles, entrapment efficiency, Miglitol, PLGA, Preformulation*

INTRODUCTION

Miglitol (MGL) is an a-glucosidase inhibitor used as oral antihyperglycaemic agent, and it is indicated for the treatment of patients with type-2 diabetes mellitus [1]. Chemically, it is (2R,3R,4R,5S)-1-(2-hydroxyethyl)-2-(hydroxymethyl) piperidine-3,4,5-triol. The dose is 25, 50 or 100 mg twice daily [2-3] . Several clinical studies have reported that MGL as monotherapy and in combination with other antidiabetic drugs is effective and ultimately reduces cardiovascular risk in cases of metabolic syndrome,[4-5] and doses of these agents can be adjusted accordingly [6]. The majority of adverse effects associated with MGL treatment involve disturbances of the gastrointestinal tract. Additionally, MGL has been reported to have a short elimination halflife (2 h),[7] requiring that it be administered in multiple doses daily; thus, there is an immense need to design and formulate new drug delivery systems that would effectively sustain the release of MGL, which would help to reduce the dosing frequency and adverse effects.

Preformulation commences when a newly synthesized drug shows sufficient pharmacologic promise in animal models to warrants evaluation in man. These studies should focus on those physicochemical properties of the new compound that could affect drug performance and development of an efficacious dosage form. A thorough understanding of these properties may ultimately provide a rational for formulation design, or support the need for molecular modification [8].

The aim of this study was to determine some of the physicochemical properties such as solubility, pKa, dissolution, melting point, assay development, stability in Solution, stability in solid state, microscopy, bulk density, flow properties and excipient compatibility.

MATERIALS AND METHODS

Miglitol (99.1%) donated by Hetero Labs Ltd, Baddi, India and PLGA (50:50) was procured from Sigma Aldrich, St.Louis Acetone, tween 80, acetonitrile (ACN) of HPLC grade and dipotassium hydrogen phosphate and phosphoric acid were of analytical-reagent grade supplied by M/S SD Fine chemicals, Mumbai, India. The HPLC grade water was prepared by using Milli-Q Academic, Millipore, and Bangalore, India. Shimadzu (Tokyo, Japan) model which consisted of a LC10AD and LC10 ADvp solvent delivery module, UV detector, a Rheodyne injector (model 7125, USA) valve fitted with a 20 µl loop, and UV detector. The system was controlled through a system controller (SCL-10A) and a personal computer using a Shimadzu chromatographic software (LC Solution, Release 1.11SP1) installed on it was used for the assay of Miglitol. All chemicals used in the study were of analytical grade and used without further purification.

Experimental Studies

Determination of solubility

The Miglitol evaluated for solubility in water, acetone, methanol, diethyl ether chloroform and ethanol in accordance with the British pharmacopoeia specifications [9, 10].

pH Determination

This was done by shaking a 1%w/v dispersion of the sample in water for 5 min and the pH determination using a digital pH meter (model 335, Systronics, India) [11]. The data presented here is for triplicate determinations.

True density

True density of Miglitol was determined by liquid displacement method. It is calculated from the volume of

intrusion fluid (toluene) displaced in the pycnometer by a given mass of powder [8].

$$D = \left(\frac{M}{Vp - Vi}\right)$$

Where, D is true density, Vp is the total volume of the pycnometer and Vi is the volume of intrusion fluid in the pycnometer containing the mass of powder (M). All the estimations were done in triplicate and average are reported in table 1.

Determination of bulk density, bulkiness and compressibility index

The bulk density of Miglitol was determined by the three tap method [12]. 10g of Miglitol powder was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped onto a hard wood surface 3 times from a height of 1inch at an interval of 2 seconds. The bulk density was obtained by dividing the weight of the sample by volume of the sample contained in the cylinder. Reciprocal of bulk density or the specific bulk volume gave the bulkiness. The percent compressibility index (I) [13] of the Miglitol was calculated using following formula and the results are given in Table1.

Compressibility Index $= 100(V_o - V_F)/ V_o$

V_o =Unsettled apparent Volume

V_F = Final Tapped Volume

Angle of repose

The static angle of repose, a, was measured according to the fixed funnel and free standing cone method [14]. A funnel was clamped with its tip 2cm above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameters (D) of the base of the powder cones were determined and the tangent of the angle of repose calculated using the equation:

$$\text{Tan } \theta = 2h/D$$

Where h = height of pile; D = Dia of pile

The data presented here is for triplicate determinations.

Determination of Partition Coefficient

10 mg drug was added in 50 ml of n-Octanol (pre saturated with water) and it was shaked and then 50 ml of distilled water (pre saturated with n- Octanol) was added and was shaked the mixture by mechanical shaker for 24 hours. After 24 hour both phases are separated. Absorbance was taken of both the phases and calculated the concentration in each phases [15].

Partition Coefficient $= \left(\frac{\text{Drug concentration in Octanol}}{\text{Drug concentration in water}}\right)$

Percentage of moisture loss

The Miglitol loaded nanoparticles were evaluated for percentage of moisture loss which sharing an idea about its hydrophilic nature. The nanoparticles weighed initially and kept in desiccator containing calcium chloride at 37 °C for 24 hours. When no further change in weight of sample was observed, the final weight was noted down [16, 17].

% of moisture loss $= \left(\frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}}\right) \times 100$

Dissolution test

In vitro dissolution studies were carried out using a dissolution apparatus USP (Paddle type) at a paddle speed of 50 rpm. The dissolution medium was 900 ml of phosphate buffer, pH 6.8, which was maintained at 37 ± 0.5°C. 5 ml of dissolution samples were withdrawn and replaced with equal volume fresh phosphate buffer, pH 6.8 at regular intervals. Collected dissolution samples were used for determination of released miglitol concentrations by using HPLC method.

Drug polymer interaction studies by FT-IR

Drug-polymer interactions were studied by FT-IR spectroscopy using the instrument Shimadzu FT-IR-8400S. The spectra were recorded for miglitol, PLGA, physical mixture of miglitol: PLGA (1:1) Samples were prepared in KBr disks (2 mg sample in 200 mg KBr) with a hydrostatic press at a force of 5.2 πcm2 for 3 minutes. The scanning range was 400 - 4000 cm2 and the resolution was 4 cm-1.

Differential scanning calorimetry

Weigh exactly 2mg of miglitol and transfer it in to standard aluminium pan cover with aluminium lid and crimp the pan using crimper. PLGA with miglitol sample prepared by weigh exactly 2mg of mixture of PLGA and miglitol, transfer it in to standard aluminium pan cover with aluminium lid and crimp the pan using crimper. Formulation excipients with miglitol sample prepared by excipients mixtures with miglitol, transfer it in to standard aluminium pan cover with aluminium lid and crimp the pan using crimper. Then subject to programmed temperature changes using differential scanning calorimetry.

Preparation of Nanoparticles

Miglitol loaded PLGA nanoparticles were formulated by double water-in-oil-in-water (W/O/W) emulsification method. 100 mg of Miglitol was dissolved in 4 ml of water. (Water phase) Varying quantity of PLGA (50:50) was dissolved in the varying quantity of dichloromethane.(Organic Phase). This water and organic phases was emulsified by using high shear homogenizer at 10000 RPM for 3 min to form primary w/o nanoemulsion. 0.2% w/v Pluronic F68 solution was obtained by dispersing the weighted surfactant in water under magnetic stirring at room temperature. Varying quantity of Eudragit L100-55 solution was obtained by dissolving the weighted polymer in 10 ml Ethanol under stirring at room temperature. The above formed w/o primary nano emulsion was subsequently transferred in the 150 ml of aqueous phase containing 0.2 % w/v pluronic F68. This mixture was emulsified by using high shear homogenizer at 24000 RPM for 3 min to form w/o/w nanoemulsion. While Homogenization, Eudragit L100-55 solution was added slowly. The resulting W/O/W emulsion was stirred with the magnetic stirrer for overnight at room temperature to allow solvent evaporation. The nanoparticles suspension was centrifuged at 13,000 RPM for 30 min at 4ºC using high speed centrifuge. The NPs were obtained by centrifugation washed with water. The Miglitol

nanoparticles were lyophilized using 2% D-mannitol as cryoprotectant.

Encapsulation efficiency (EE)

Drug loaded nanoparticles (100 mg) were powdered and suspended in water and then sonicated for about 20 minutes. It was shaken for another 20 minutes for the complete extraction of drug from the nanoparticles. The mixture was filtered through a 0.45 µm membrane filter (MILLIPORE). Drug content was determined by UV-visible spectrophotometer (UV – 160IPC, Shimadzu, Japan) at 232 nm. The percent entrapment was calculated using the following formula [33]. The results are given in Table 7,

$$\text{Encapsulation efficiency} = \left(\frac{\text{Actual weight of drug in sample}}{\text{Nanoparticles Sample Weight}}\right) \times 100$$

Particle Size Analysis of Nanoparticles

Average particle diameter and size distribution of nanoparticles were determined by laser diffractometry using a Mastersizer 2000 (Malvern Instruments, Malvern, UK). Approximately 10 mg of nanoparticles were dispersed in 2 to 3 ml distilled water containing 0.1% Nonidet P40 for several minutes using an ultrasonic bath. Then, an aliquot of the nanoparticle suspension was added into the small volume recirculation unit [32], which was subsequently circulated 3500 times per minute. Each sample was measured in triplicate for the analysis. Particle size was expressed as the weighted mean of the volume distribution.

RESULTS AND DISCUSSION

Particle size distribution of drug has influence on many bulk properties of pharmaceutical interest such as flow properties, packing, packing densities, compressibility segregation characteristics etc. Hence, it must be the aim of pharmaceutical technologist to study the particle size distribution. The particle size distribution of miglitol nanoparticles was shown in Fig 1.

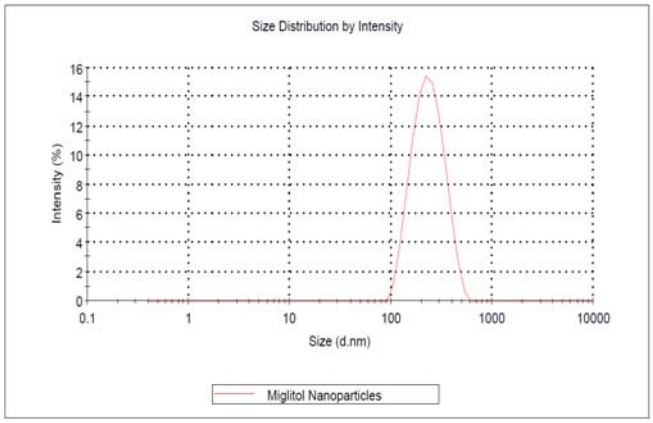

Figure 1: Particle size of Miglitol loaded nanoparticles

The results of solubility, true density, bulk density, compressibility index, angle of repose, moisture content, pH, Partition Coefficient are given in Table 1.

Table 1: physicochemical properties of Miglitol

Parameters	Results
Description	Miglitol occurs as white to off white powder.
Solubility	Soluble in water. Solubility of Miglitol in pH 1.2 was found to be 30.51mg/ml Solubility of of Miglitol in pH 6.8 was found to be 31.09mg/ml Solubility of Miglitol in pH 7.4 was found to be 30.67mg/ml As evident from the solubility profile study, Miglitol was soluble in pH 1.2, pH 6.8 and pH 7.4
pH	8.8
True density (gm/cc)	1.41 ± 0.23
Bulk density (gm/cc)	0.71± 0.02
Compressibility Index (%)	19.52± 0.62
Angle of repose (°)	39.4± 1.15
Moisture content (%)	0.4 ± 0.1
Partition Coefficient	1.2± 0.45
Melting Point (°C)	145.44
pK_a	5.9

The dissolution rate of Miglitol of tablets was over 95% after 30 min (***Fig 2***).

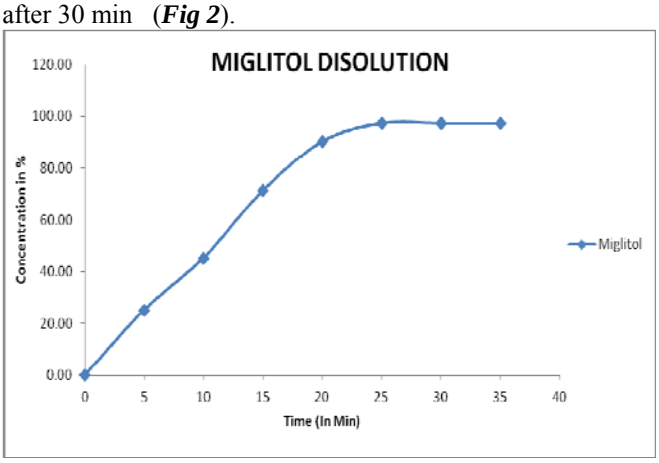

Figure 2: Dissolution rate of Miglitol

Drug –Excipients accelerated compatibility study based physical observation and assay confirms no colour change was observed. Based on the chemical evaluation it was found that there was no significant change observed indicating that the drug is compatible with the added ingredients. The results of this study were given in Table 2 to 4.

Table 2: Physical characteristics of individual drug and excipients

S.No	Sample ID	Initial description	Final description
1.	Miglitol	White crystalline powder	No change
2.	PLGA	Fine white crystalline powder	No change
3.	Pluronic F68	Fine white powder	No change
4.	Eudragit	Fine white powder	No change

Table 3: Physical characteristics of drug-excipient mixture

S.No	Sample ID	Initial description	Final description
1	Miglitol	White crystalline powder	No change
2	Miglitol+ PLGA	White crystalline powder	No change
3	Miglitol+ Pluronic F68	Fine white powder	No change
4	Miglitol+ Eudragit	Fine white powder	No change

Table 4: Chemical characteristics of drug-excipient mixture

S.No	Sample ID	Initial assay (%)	Final assay (%)
1.	Miglitol	99.87	99.85
2.	Miglitol+ PLGA	99.83	99.82
3.	Miglitol+ Pluronic F68	99.84	99.83
4.	Miglitol+ Eudragit	99.82	99.82

The drug-excipient compatibility studies employing DSC has been carried out to confirm the inertness of Pharmaceutical excipients. In this study we have chosen the polymer for the preparation of polymeric nanoparticle is PLGA and Eudragit L100-50 Concentration. Hence before going to the preparation of formulation we need to confirm the compatibility. DSC studies confirm the chemical inertness of the PLGA and Eudragit L100-50 Concentration polymers with the drug miglitol. From the results obtained we can conclude that PLGA polymer and Eudragit L100-50 Concentration polymer is compatible with the drug miglitol to formulate Nano formulation.

Compatibility study using IR

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.

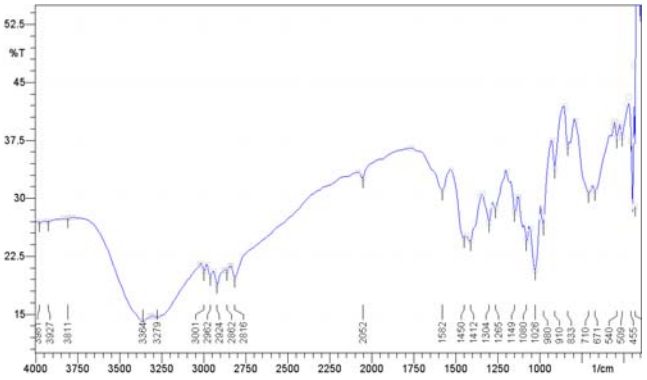

Figure 3: IR spectrum of Miglitol sample

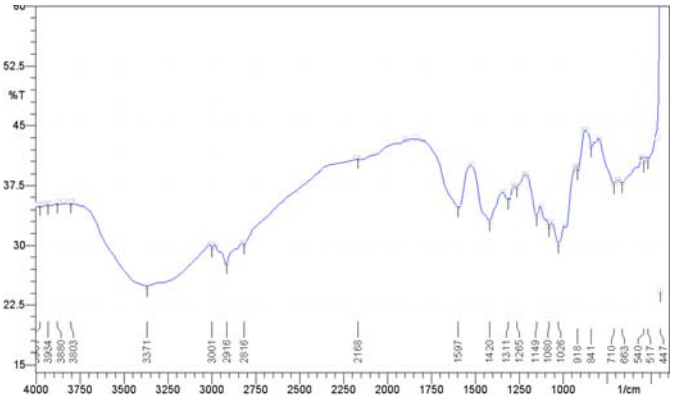

Figure 4: IR spectrum of blend of Miglitol nanoparticles

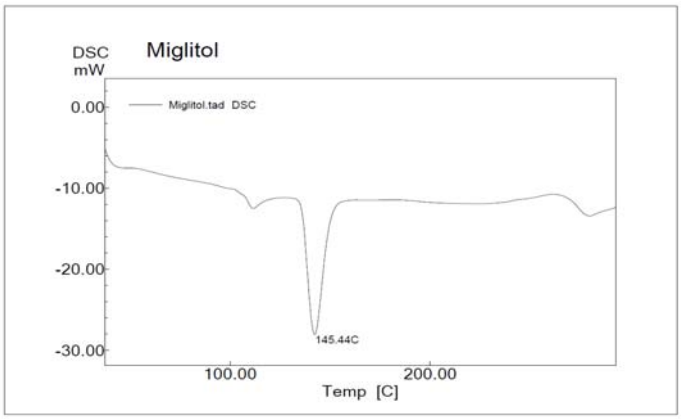

Figure 5: DSC thermogram of miglitol

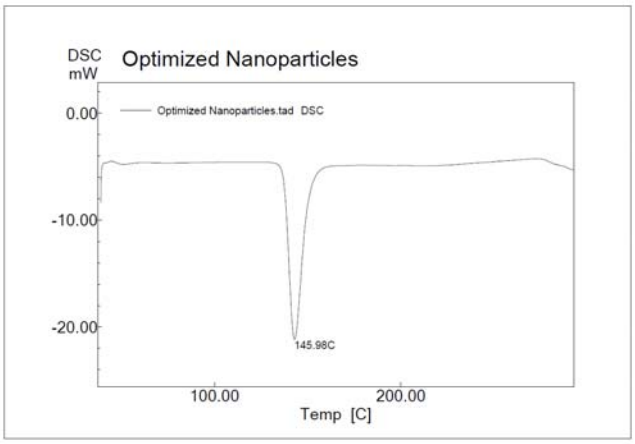

Figure 6: DSC thermogram of miglitol nanoparticles

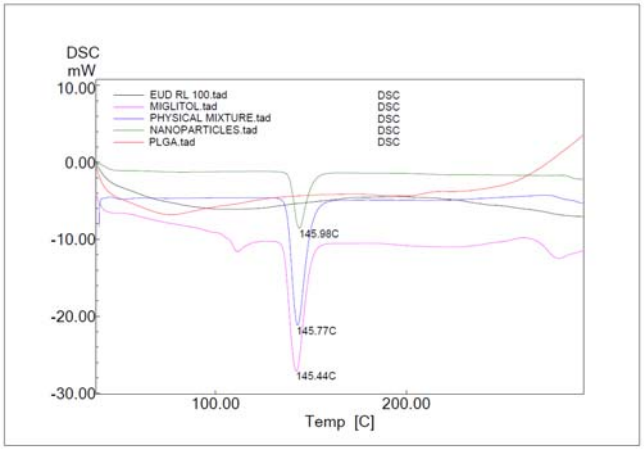

Figure 7: DSC thermogram of Multiview

CONCLUSION

The preformulation phase is a critical phase in establishing the properties of CDs that will allow suitable risk assessment for development. Typically it begins during the lead optimization phase, continues through prenomination, and on into the early phases of development. Decisions made on the information generated during this phase can have a profound effect on the subsequent development of those compounds. Therefore, it is imperative that preformulation should be performed as carefully as possible to enable rational decisions to be made. The quantity and quality of the drugs can affect the data generated as well as the equipment available and the expertise of the personnel conducting the investigations. In this study we successfully completed the physicochemical characterization of miglitol properties like morphology, size, solubility, pH, Partition coefficient, Surface area flow property, drug content and release study. This knowledge can be useful in developing modified release formulations mainly sustained release formulation of miglitol loaded nanoparticles.

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