International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 2104-2114 www.ijprajournal.com ISSN: 2456-4494

Design, Development and Characterization of Magnetic Microspheres of Metronidazole by using Ocimum Basilicum Mucilage.

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Date of Submission: 08-06-2024 Date of Acceptance: 18-06-2024

ABSTRACT:
The magnetically controlled drug delivery targeting method, which aims to deliver the drug at a rate determined by the needs of the body during the course of treatment. The main aim of this study was to design, develop and characterize the magnetic microspheres of Metronidazole by using Ocimum basilicum mucilage as a natural polymer. The study involved preparation of magnetic microspheres of Metronidazole by ionotropic gelation method. The microspheres were characterized in terms of particle size, percentage yield, drug content, drug entrapment efficiency and In- vitro release pattern. Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC) of drug and polymer was taken to visualise the compatibility of drug and polymer. Scanning electron microscopy (SEM) shows the morphological analysis. From the study, we successfully developed micro particulate drug delivery system of Metronidazole by using natural polymer like Ocimum basilicum mucilage and rate retardant sodium alginate polymer.

KEYWORDS: Magnetic, Ocimumbasilicum, Metronidazole, sodium alginate.

I. INTRODUCTION:

Pharmaceutical research and innovation are focusing more and more on distribution strategies that maximize positive effects while enhancing intended therapeutic outcomes[1].Recently, a number of innovative drug delivery methods have been developed to reduce medication loss and degradation, avoid negative side effects, boost bioavailability, and enable controlled and targeted drug delivery. One of the most recent approaches in the pharmaceutical industry is magnetic microsphere because of their ability to easily modify the surface and the magnetic characteristics. Due to their magnetic characteristics, these particles have a new dimension that allows for manipulation when an external magnetic field is applied. This characteristic pave the way for new applications in which pharmaceuticals tied to magnetic particles supply the drug at a rate determined by the body's requirements during the course of treatment[2].

In magnetic targeting, a therapeutic radioisotope or medicine is attached to a magnetic substance, injected into the patient's bloodstream, and then halted with a strong magnetic field in the desired location. Materials included into magnetic carriers, such as magnetite, iron, nickel, cobalt, neodymium-iron-boron, or samarium-cobalt, give them their magnetic responsiveness to a magnetic field. In order to reduce renal clearance and boost target site specificity, magnetic microspheres were created [3].

The Ayurvedic medical system is widely used and accepted by people worldwide, not justin India, but also in the developed nations of the USA, Europe, China, Japan, Canada, etc.The therapeutic and fragrant qualities of Ocimum basilicum are highly prized in both ancient and contemporary medical systems. Ocimum contains aromatic herbs, bushes, and shrubs that produce essential oils of different scent compounds. These essential oils are extremely valuable in the pharmaceutical, contemporary the perfume industry, and food processing industries[4,5].

It is possible to use Metronidazole, a nitroimidazole antibiotic, to treat a range of anaerobic bacteria and protozoa. It is frequently used as a supplemental therapy for infections in spite of that some incidences of severe neurotoxicity of Metronidazole are reported[6].

II. MATERIALS AND METHOD:

The seeds of Ocimum basilicum was purchased from local vender, Satara. Metronidazole was obtained as a gift sample from Therawin formulation Ambala city, Haryana. All other reagents were of analytical grade and purchased from loba chemie Pvt Ltd, Mumbai.

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Isolation and purification of O. basilicum mucilage:

O. basilicum were cleaned by washing with distilled water and soaked in 500 ml of distilled water for 12-14 h until they become soft. The soft seed material was subjected to slow stirring using the mechanical stirrer. Seedless white coloured mucilaginous material was collected by filtering the seeds through muslin cloth. Collected mucilage was purified by precipitation with 250 ml of ethanol. The precipitated mucilage was dried in the oven at 50-55^{0}C for 4-5 h. Dried mucilage scraped with spatula, powdered in mortar and pestle, sieved through a mesh no. 60 andstored in desiccator for further studies[7].

Characterization of isolated O. basilicum mucilage:

Product yield was determined to check the efficiency of method of isolation. The yield of mucilage was determined by weighing the dried extracted mucilage. Yield = 100×mass of extracted gum(g)/mass of seeds(g).

The mucilage samples were studied for various phytochemical screening tests to confirm the nature of mucilage obtained. Isolated mucilage samples were evaluated for organoleptic parameters such as color, odor and taste. Loss on drying is loss of mass expressed as percent w/w. An properly weighed quantity (5 g) of mucilage was placed in a tarred porcelain and dried in an oven at 110° for 2 hours until a steady weight was obtained. It was then cooled to room temperature in a desiccator, weighed, and recorded. The following equation was used to compute the percentage: loss on drying (%) = loss in weight of the sample/weight of sample×100.

Determination of ash value:

Ash values indicate the quality and purity of a crude medication, particularly in the form of powder. The goal of ashing vegetable medications is to remove all residues of organic debris that may interfere with analytical analysis. When crude pharmaceuticals are incinerated, they typically produce an ash composed of carbonates, phosphates, and sodium, potassium, calcium, and magnesium silicates. A greater limit of acid-insoluble ash is imposed, especially when silica is present or the drug's calcium oxalate level is very high

Swelling capacity: The amount of space occupied by 1 g of medication in milliliters, including any adhering mucin after it has swollen in 4 hours in an aqueous liquid. A 25 ml ground glass stoppered cylinder containing 1 gm of mucilage was graduated across a height of 120 to 130 mm in 0.5 divisions. This was mixed with 25 ml of distilled water, vigorously shaken every ten minutes for one hour, and then let to stand for 24 hours. It was calculated how much space the dissolving agent and adherent mucilage took up. The mean of three measurements was used to determine the swelling index [7]

III. FORMULATION OF MAGNETIC MICROSPHERES:

Sodium alginate (SA), Ocimum basilicum mucilage (OBM) and Magnetite were dissolved in distilled water (29ml) to form a homogeneous polymer solution. The active core material Metronidazole was added to the polymer solution and mixed thoroughly with a using magnetic stirring for 30 min stirrer to form a smooth viscous dispersion. The resulting dispersion was then added drop wise into calcium chloride (10 %w/v) solution through a syringe with a needle of size No: 21. The added droplets were retained in the calcium chloride solution for 15 min to complete the curing reaction and to produce spherical rigid microspheres. The microspheres were collected by decantation and the product, thus separated was washed repeatedly with distilled water and dried at 37°C for overnight. The dried microspheres were stored in a desiccator until used [8]

3.1 Experimental design for optimization

In order to obtain "best" or an "optimized product" nine different formulations weregenerated using 3^2 factorial designs. The amount of sodium alginate (X_I) andamount of Ocimum basilicum mucilage (X_2) were taken as independent formulationvariables while % drug content (Y_1). % Entrapment efficiency (Y_2) and % drugrelease at 8 hr (Y_3) were considered as dependent or response variables. Astatistical model incorporating interactive and polynomial terms was used toevaluate the responses. Design Expert (Version 13.0.0) Stat-ease software was usedfor the generation and evaluation of the statistical experimental design. The effectsof independent variables were modeled using a quadratic mathematical equationgenerated by a 3^2 factorial design such as

$$Y= b +b X +b X +b X X +b X^2 +b X^2$$

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Where Y is the response; b, is the intercept, and b_1, b_2, b_{12}, b_{11}, b_{22} are regressioncoefficients. X_1 and X_2 is individual effects.

Table no 1: Design Layout of levels of 3^2 factorial batches

Batch	SA (mg)	OBM (mg)	Metronidazole(mg)	Magnetite(mg)
F1	225	325	500	30
F2	225	350	500	30
F3	225	375	500	30
F4	250	325	500	30
F5	250	350	500	30
F6	250	375	500	30
F7	275	325	500	30
F8	275	350	500	30
F9	275	375	500	30

III.2

III.3 Characterization of Magnetic Microspheres of Metronidazole:

Percentages yield:

The yield of microbeads was determined by comparing the whole weight of microbeads formed against the combined weight of the copolymer and drug.% yield = (Total weight of microspheres obtained / total weight of powder)×100[37]

Drug content estimation:

Accurately weighed microspheres were digested with phosphate buffer and analysed for drug content.[38]

Drug entrapment efficiency:

Magnetic microspheres equivalent to 10 mg were weighed and crushed using a glass mortar and pestle.The crushed powdered microspheres weresuspended in 10 mL solution (0.5 mL 0.1 N HCl + 9.5 mL PBS) for 5 min. The suspension was then filtered. Measuring the absorbance at 277 nm by UV-Vis spectrophotometer (UV1800 Shimadzu) after appropriate dilutions with PBS.

Entrapment efficiency = Experimental drug content / Theoretical drug content × 100. [6]

In vitro drug release study :

Drug release tests were performed according to USP XXIV paddle method for each size fraction separately. Accurately weighed amounts (100 mg) of microspheres were introduced into 900 mL of PBS (phosphate buffer saline, pH (7.4) and stirred with 100 rpm at (37 ^{0}C). Five milliliters samples were withdrawn and filtered at selected time intervals. The concentration of Metronidazole was determined spectrophotometrically at 277 nm. [6]

Fourier transforms infrared spectroscopy (FTIR): Fourier transform infrared spectra were obtained using BRUKER FTIR spectrometer. Samples of Metronidazole, polymer, physical mixtures and optimized formulation of microsphere were taken for the study. by studying the IR spectra it will help in identifying the functional groups. [21]

Scanning Electron Microscopy and Morphology Characterization (SEM):

The surface morphology and internal texture of the microspheres were studied by scanning electron microscopy. Scanning Electron Microscope JSM 6330 JEOL (Japan). Acceleration voltage set at 3Kv at Magnification level 45x, 70x, 95x, 200 x. The microspheres are mounted directly on the SEM sample stub, using double-sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr) and photographed.[7]

X-ray diffraction (XRD): XRD patterns were recorded using ULTIMA IV,fitted with a copper target, a voltage of 40 kV, and a current of 40mA. The scanningrate was 1/min over a 2 ^{0} range of 10-80°. XRD patterns were traced for Metronidazole,

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physical mixture and formulation. The samples wereslightly ground and packed into the aluminum sample container.[14]

Differential scanning calorimetric (DSC): Thermal analysis of microcapsule and its component can be doneby using differential scanning calorimetry (DSC), thermo gravimetric analysis (TGA), differential thermometric analysis (DTA) Accuratelythe sample was weighed and heated on alumina pan at constant rate of10°C/min under nitrogen flow of 40ml/min.[12]

IV. RESULTS AND DISCUSSION

The dried and coarsely powdered Ocimum basilicum mucilage yielded 12% of dried powder.mucilage showed presence of carbohydrates, non-reducing sugar, hexose sugar, pentose sugar, starch, alkaloids and mucilage. Physicochemical parameter helps to judge the identity and purity of plant derived drugs. It is commonly applied parameter for detection of impurities, adulteration and substitution of drug. The swelling property of mucilage powder is good. The FT-IR of OBM was taken. The prominent peak of OBM are shown in figure 1.

Table no 2: Results of Phytochemical examination of mucilage

Name of test	Reagents	Observation	Inference
Mucilage test	Rheudenium red	Red colour	mucilage present
Mucilage test	Aq.koh/water	Powder swell	mucilage present
Molish's test +Conc.H_2SO_4junction	Alpha napthol+alcohol	Violet ring at	Carbohydrate present
Pentose test	HCL+ crystal of phloroglucinol	Red colour	Pentose sugar present
Hexose test cobalt chloride	Tollens phloroglucinol greenish blue colour	Yellow-red colour glucose present	Hexose sugar,
Non-reducing test Benedict's test	Fehling's and in colour	No change sugar present	Non-reducing
Starch	Iodine	Blue colour	Starch present
Alkaloid	Dragendorff's	Orange-Brown ppt	Alkaloid present
Alkaloids	Hager's	Yellow ppt	Alkaloid present

Absence of glycosides, steroid, and tannins confirming the absence of these within isolated mucilage as shown in table no 2.

Table no 3: Physicochemical analysis of mucilage

Parameter	OBM
Loss on drying	5%
Ash value	8.2%
Viscosity	14.33cps
Swelling index	10.04%

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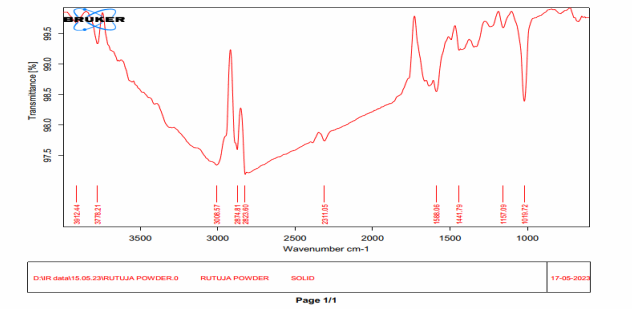
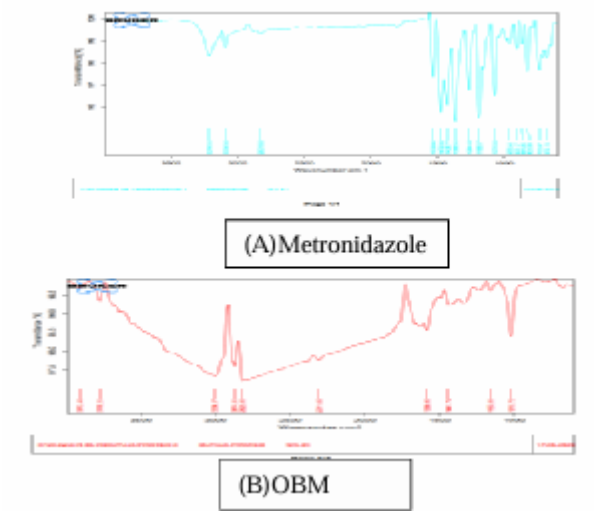


Figure no 1- FTIR of mucilage

Fourier transforms infrared spectroscopy (FTIR):



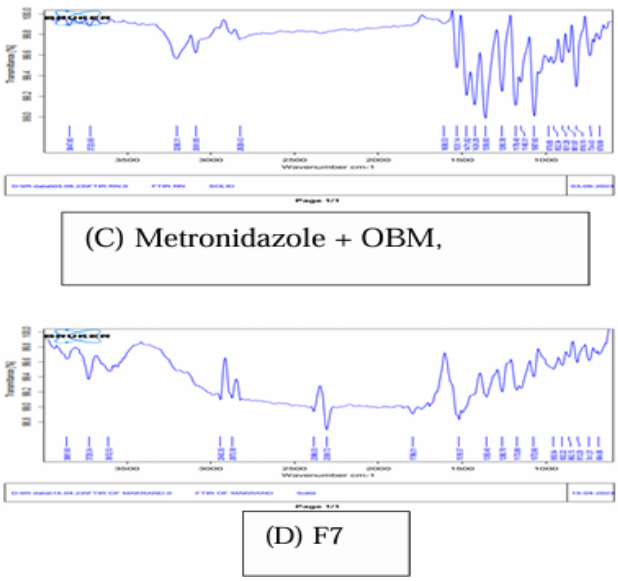


Figure : FTIR spectra of A) Metronidazole B) OBM C) Metronidazole + OBM, D) F7

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The IR spectrum of the formulation showed that there is no significant evidence forinteraction between drug and the polymer. Peaks of both drugs as well formulation were observed and interpreted. So, this clearly suggests that drug, polymers and excipients used for the current study were compatible. There is no significant or any shift in positions of the characteristic absorption bands of drug in the formulations.

Scanning Electron Microscopy and Morphology Characterization (SEM):

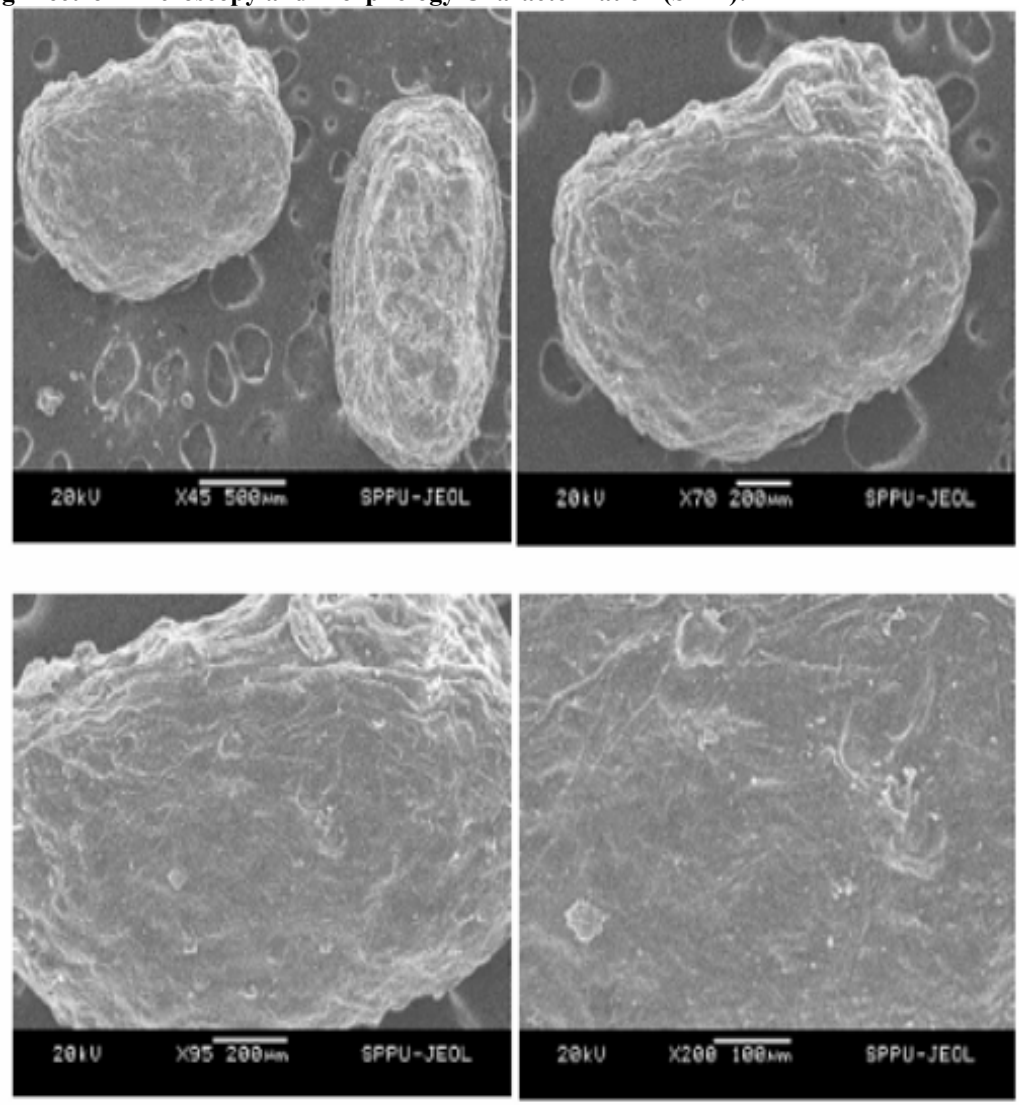

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Figure: Scanning electron photograph of drug loaded microspheres (Magnification, X45, X70, X95 and X200)

SEM photomicrographs of optimized formulation F7 microspheres were rough surface, shows few pores on surface. Particulate matter of the drug and polymer were seen on the surface of the microspheres, indicating uniform distribution of the drug in the polymeric network. Further more the microsphere was not hollow. shown in figure.At higher magnification it shows slight rough surface

X-ray diffraction (XRD):

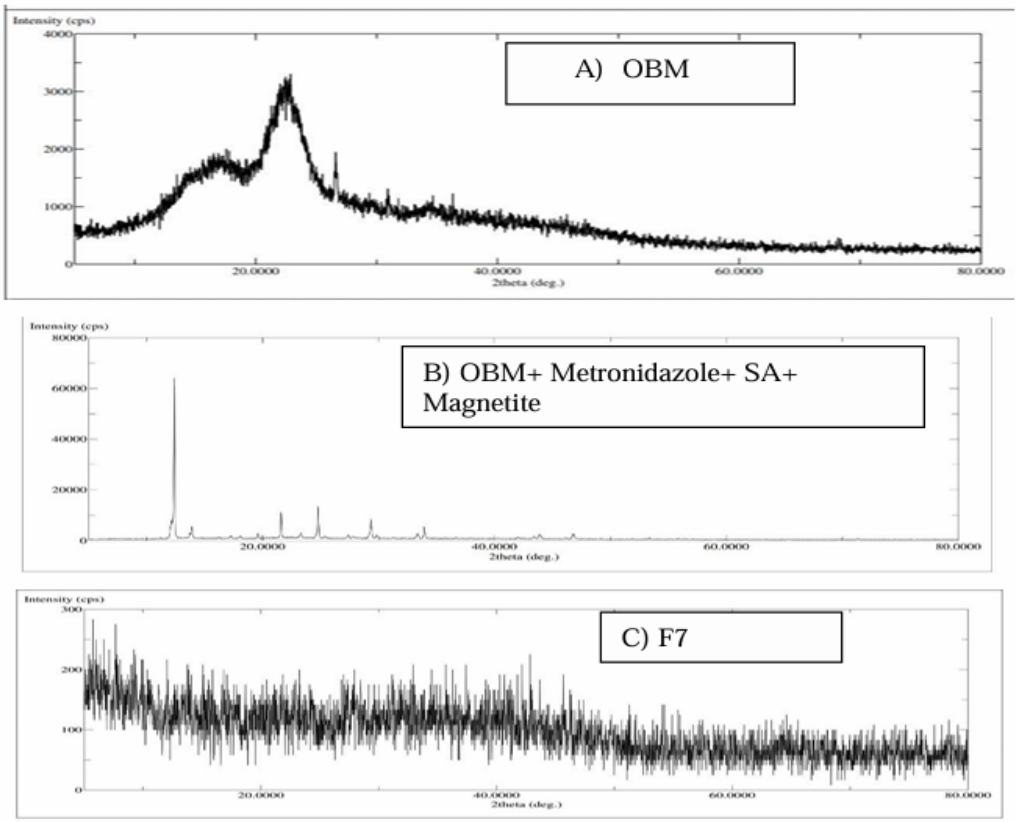

Figure XRD spectra of A) OBM, B) OBM+ Metronidazole+ SA+ Magnetite (s) F

The Metronidazole has crystalline characteristics which are represented by peaks in X-ray diffractograms, and the most evident peaks appear at $2\theta^{0}$, 13, 17, 18 and 19. These peaks were not observed in the Metronidazole loaded microspheres. This indicates that drug particles are dispersed at molecular level in the

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polymer matrices since no indication about the crystalline nature of the drugs was observed in the drug loaded microspheres [40].

Differential scanning calorimetric (DSC):

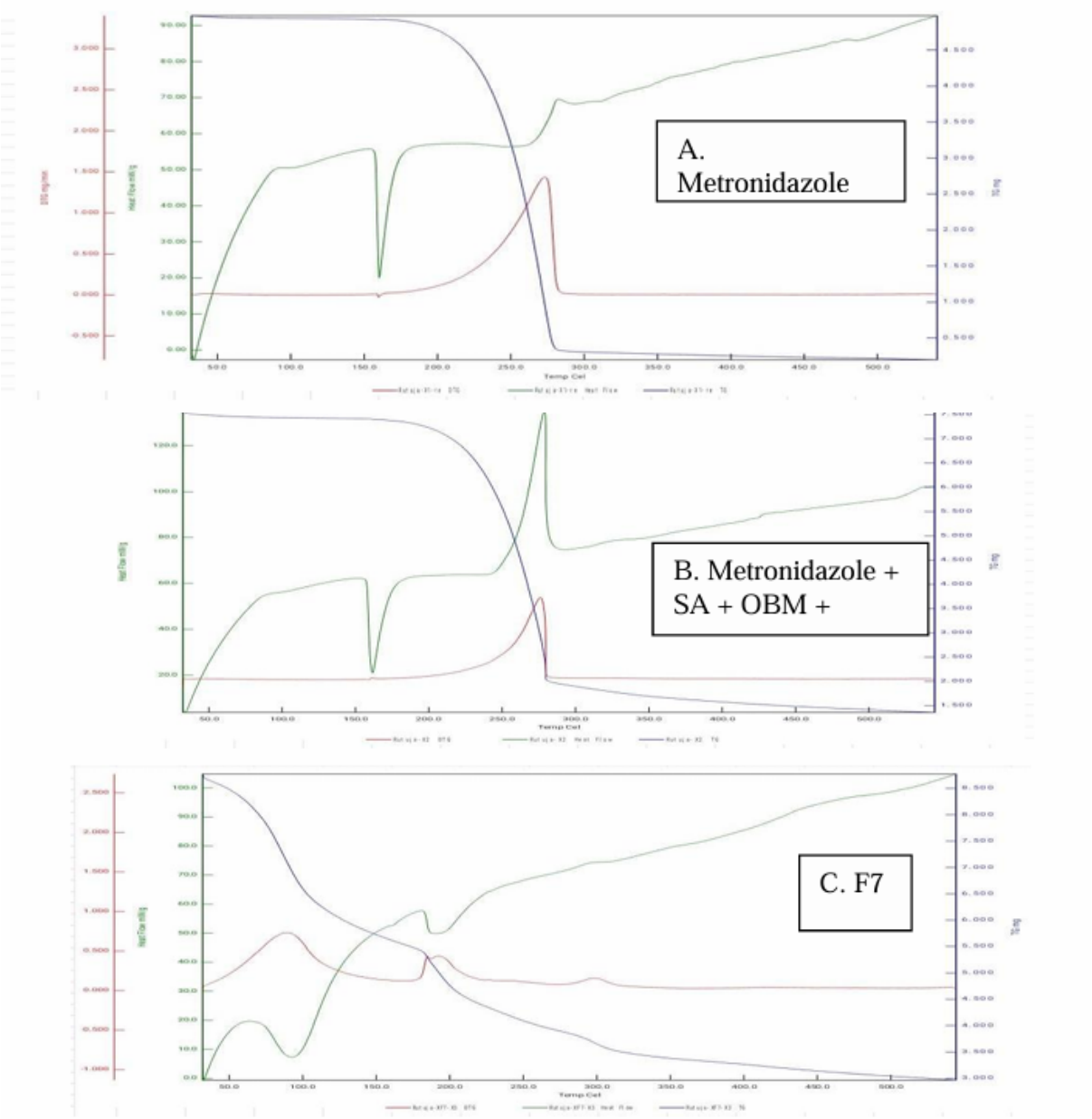

Figure DSC of A) Metronidazole B) Metronidazole + SA+OBM+Magnetite C) F7

The DSC thermograms obtained individually for Metronidazole and physical mixture its formulations. The thermograms of Metronidazole shows an individual solitary sharp melting endothermic peak between 158-160°C corresponds to melting point indicate that drug exists in single crystalline state and the physical mixture of Metronidazole, there is no any type of physical interaction was observed. Formulation F7, shows endothermic peaks were observed between 180-190°C. The thermograms of Metronidazole and optimized formulation F7, no any type of physical interaction was observed between the formulation excipients and pure drug.

V. CONCLUSION

From the present study it was concluded that magnetic microsphere of Metronidazole by using Ocimum basilicum mucilage can be prepared using the ionotropic gelation method. The preparation process was simple, reliable, and inexpensive. 3^2 full factorial designs were used to study the effect of process variables on formulation characteristics by applying statistical analysis. FTIR, XRD and DSC analyses apparently did not indicate any interaction of the drug with the polymers. However, the drug content, drug entrapment efficiency and morphology of the microsphere were found to be influenced by the method of preparation, composition of microsphere as well as exposure to the cross-linking agent. The microsphere formed was shrinkage in shape as evidenced by SEM photographs. In vitro drug release study showed that drug release can be modified by varying drug to polymer ratio. The release rate was found to be increased in accordance with the increase in the ratio of polymer used.

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