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FORMULATION & EVALUATION OF FLOATING MICOSPHERE OF RANITIDINE HYDROCHLORIDE

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Abstract:

The present study was to formulation & evaluation of floating microsphere of ranitidine hydrochloride. The physical characteristic like organoleptic properties of drug sample was performed and it was found to be bitter in taste, colour was white crystalline powder and was odourless. And hence the drug sample was found to be as per specifications. The quantitative solubility of drug was determined and it was found that drug freely soluble in methanol and ethanol, sparingly soluble in chloroform and slightly soluble in water. And this result indicated that the drug is poorly water soluble and soluble in organic solvents like methanol and ethanol. The partition coefficient of drug was determined as per procedure. It was found to be 2.50 that indicated that the drug was portioning maximum in lipophillic phase and hence it was found that drug was lipophilic in nature. Identification and authentication of drug sample was done by infrared spectroscopy. The IR spectra showed the presence of principal groups like at 756 o- disubstituted benzene; 1279 C-N; 1458 & 1479 CH3; 1531 C=C aromatic; 1638 C=N, C=O ring and at 3410 H_2O. The principal groups of infrared spectroscopies showed that the drug sample was authenticated. Identification and authentication of drug sample was done by ultraviolet spectroscopy and it was scanned in the range of 200-400 nm. Drug absorption maximum λ_{max} was found to be at 310 nm. Absorption maximum showed that drug sample was authenticated. Melting point was also determined by melting point apparatus. The melting point was found in the range between 226^0-237^0C which meets as per specification. The melting point showed that drug sample was authenticated.

***Keywords**: Microsphere, dosage form, drug delivery, design, bioavailability*

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INTRODUCTION:

Controlled drug delivery technique presents front line part of today's developed technique, in this includes many scientific approaches, serving for individual care. The drug deliverance technique having abundant advantages than existing conventional type of dosage, it involves enhanced effectiveness, minimized poisoning, enhanced consumer conformity also ease. This type of drug deliverance technique utilizes micro molecules, for caring drugs. As the varieties of forms for dosage are invented like microparticle as well as nanoparticles shown more significance.

An ideal and advanced oral drug delivery system is that, which exactly controls speed, time as well as site of release of medicament separately of normal physiological variables such as gastrointestinal tract pH, digestive condition of the gastrointestinal tract, peristalsis movement and circadian rhythm. Advance in polymer science and technology outcome in pick up the pace research and developmental activity in the design of drug delivery devices. Therapeutic effectiveness of a drug depends upon the bioavailability and eventually upon the solubility of drug substances. Solubility is prerequisite to achieve desired concentration of drug in systemic circulation, drug absorption and pharmacological response. Oral route of drug administration is the uncomplicated and easiest approach of administration of drugs as it offers good patient compliance, convenience, accurate dosing, easy production, and greater stability. Poor hydrophilic drugs encompass dissolution is rate restrictive step in the process of drug absorption (1-3). Imminent bioavailability exertions are prevailing with extremely hydrophobic drugs due to inconsistent or partial absorption from gastrointestinal tract (GIT).

Bioavailability is the most important property of a dosage form. It is the ability of the dosage form to deliver the active ingredient to its site of action in an amount sufficient to elicit the desired pharmacological response. Bioavailability is defined more precisely as the rate and extent of absorption of a drug from its dosage form in to the systemic circulation. It is affected by a number of factors related to the drug, dosage form and patient (4-5).

Dosage form related factors which can produce profound differences in the drug bioavailability include formulation and manufacturing variables such as particle size, the chemical form, solubility of the drug, the type and quantity of excipients used, the compaction pressure etc (6).

Polymeric excipients are commonly worn for controlled release delivery systems, as a coating for drug particle by micro encapsulation technique and a matrix in which drug material can be embedded. There is an enormous selection of polymers accessible for use dosage forms. Starting from hydrophilic toward hydrophobic. Utilization of polymers in dosage forms is as miscellaneous as the polymers, in which can be natural, synthetic and semi synthetic types. All the pharmaceuticals' goods prepared for internally drug liberation by means of the orally through immediate or constant or proscribed liberate systems and the dosage forms in the form of firm dry or liquor suspension, should be manufactured under inherent uniqueness to Gastro Intestinal h to makeup, pharmacokinetics, pharmacodymics. The dosage form design is important to success a systemic step towards the victorious expansion to orally admitted products.

The fundamental rational of proscribed drug liberation is to modify pharmacokinetic as well as pharmacodynamic property of drugs, by means of novel drug delivery system.

MATERIALS AND METHOD:

MATERIALS USED

Table. 1: Materials used for preparation of Microspheres

S. No.	Materials Used	Supplier
1.	Ondansetron hydrochloride	Torent Pharmaceutical Pvt limited , Ahmedabad.
2.	Sodium alginate	Loba Chemical
3.	Eudragit RS 100	Loba Chemical
4.	Hydroxy propyl methyl cellulose	Fisher scientific
5.	Carbopol 934P	Finar scientific

INSRUMENTS USED

Table. 2: Instruments used for the preparation of Microsphere

Serial No.	Instruments	Supplier
1.	UV /Visible Spectrophotometer	Systronic Double Beam Spectrophotometric
2.	FT-IR	Bucker, (Germany)
3.	Dissolution Apparatus	EI laboratory, (H.P)
4.	Rotatory evaporator	Perfit India Pvt. Ltd
5.	Optical Microscope	Lyzer, (Haryana)
6.	Micro-Centrifugation	REMI laboratory.(Mumbai)
7.	Frans-Diffusion Cell	Sigma labs
8.	pH Meter	EI laboratory, (H.P)
9.	Brookfield viscometer	PRO-II extra model, Brookfield viscometer, USA

FORMULATION DEVELOPMENT OF MICROSPHERES

Quasi-emulsion solvent diffusion method was chosen to prepare Eudragit based microspheres.

Inner phase

To prepare the inner phase, Eudragit RS 100 was dissolved in 3 mL of methanol and triethylcitrate (TEC) was added at an amount of 20% of the polymer in order to facilitate the plasticity. The drug was then added to the solution and dissolved under ultrasonication at 35°C.

Outer phase

To prepare the inner phase PVA dissolved in 200 mL of water in a separate container.

Mixing step

The inner phase was poured into the PVA solution in 200 mL of water (outer phase). The resultant mixture was stirred for 60 min, and filtered to separate the microballons. The microballons were washed with distilled water and dried at 40°C for 24h. (D'souza J. I., 2008)

Table: 3. Formulation additives

Ondansetron hydrochloride Microspheres						
Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Inner phase						
Drug (mg)	2.5	2.5	2.5	2.5	2.5	2.5
Eudragit RS 100 (g)	0.23	0.28	0.36	0.50	0.83	2.5
Methanol (mL)	3	3	3	3	3	3
Outer phase						
Distilled water (mL)	200	200	200	200	200	200
PVA (mg)	50	50	50	50	50	50

EVALUATION OF MICROSPHERES

Determination of Production Yield and Loading Efficiency

The production yield of the microparticles was determined by calculating accurately the initial weight of the raw materials and the last weight of the microballons obtained (Kilicarslan M., 2003).

$$\text{Production Yield} = \frac{\text{Practical Mass of Microsponges}}{\text{Therotical Mass (polymer + drug)}} \times 100$$

The loading efficiency (%) of the microballons can be calculated according to the following equation:

$$\text{Loading Efficiency} = \frac{\text{Actual Drug Content in Microsponges}}{\text{Therotical drug Content}} \times 100$$

Particle Size Analysis

Particle size analysis of prepared microspheres was carried by using Malvern Particle Size Analyzer Hydro 2000 MU (A). Microballons were dispersed in double distilled water before running sample in the instrument, to ensure that the light scattering signal, as indicated by particles count per second, was within instrument 's sensitivity range.

During the measurement, particles are passed through a focused laser beam. These particles scatter light at an angle that is inversely proportional to their size. The angular intensity of the scattered light is then measured by a series of photosensitive detectors. The map of scattering intensity versus angle is the primary source of information used to calculate the particle size. The scattering of particles is accurately predicted by the Mie scattering model. The Mastersizer 2000 software, allows accurate sizing across the widest possible dynamicrange.

Scanning Electron Microscopy

For morphology and surface topography, prepared microspheres were coated with platinum at room temperature so that the surface morphology of the microballons could be studied by SEM. The SEM, a member of the same family of imaging is the most widely used of all electron beam tools (Goldstein J. I., 2003). The SEM employs a focused beam of electrons, with energies typically in the range from a few hundred eV to about 30 keV, which is across the surface of a sample in a rectangular scan pattern. Signals emitted under this electron irradiation are collected, amplified, and then used to modulate the brightness of a suitable display device which is being scanned in synchronism with probe beam.

Infrared Spectroscopy

FTIR spectroscopy was conducted using Perkin Elmer, Spectrum 100 FT-IR spectrometer. Spectrum was recorded in the wavelength region of 4000 to 400 cm-1. The procedure consisted of dispersing a sample in excess of potassium bromide nearly at the ratio 1:100, mixed well, after which the mixture was kept into the sample holder for analysis.

Differential Scanning Calorimetry (DSC)

Thermal analysis is an important evaluation technique to find any possible interaction between the drug and used polymers. Any of such interaction may reduce the drug entrapment efficiency of the polymer and may also alter the efficacy of the drug. Such interaction can be identified by any change in thermogram.

***In-vitro* Release Study of Microspheres**

Accurately weighed loaded microspheres (5 mg) were placed in 50 ml of ethanol/methanol in 100 ml glass bottles. The later were horizontally shaken at 37°C at predetermined time intervals. Aliquot samples were withdrawn (replaced with fresh medium) and analysed UV spectrophotometrically at 310 nm for Ondansetron hydrochloride. The contents of drugs were calculated at different time intervals up to 6hrs.

Stability Profile of Microspheres Formulation

The purpose of stability testing is to provide evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. (Vadas E. B., 2000)

Stability profile of the active component is the major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity. However, the studies take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines.

RESULT AND DISCUSSION:

PREFORMULATION STUDY

Preformulation testing is the first step in the rational 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 combination with excipients.

Physical Characteristics Organoleptic properties:

Colour**:** A small quantity of drug powder was taken on butter paper and viewed in well-illuminated place.

Taste and odour: Very less quantity of drug was used to get taste with the help of tongue as wellas smelled to get the order.

Table: 4. Organoleptic and physical properties of drug sample

Test	Observations
Colour	White off-white crystalline solid powder
Taste	Characteristic
Odour	Odourless

Solubility

A qualitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or *vice-versa*. After each addition, the system was vigorously shaken and observed visually.

Table 5. Solubility profile of drug sample

S. No.	Solvents	Solubility
1.	Water	Soluble (+++)
2.	DMSO	Soluble (+++)
3.	Methanol	Soluble (+++)
4.	Ethanol (95%)	Freely soluble (++++)
5.	Chloroform	Slightly soluble (++)

Partition coefficient

For the determination of partition coefficient 25 µg/ml solution of pure drug in n-octanol was prepared. Then the mixture of n-octanol and water were mixed in ratio of 1:1. Then this mixture was mixed properly for 30 minutes. Further the mixture was allowed to stand for one hour. After this the mixture was centrifuged at 5000 rpm at 25^{O}C. Mixture was than separated and the absorbance of individual phases of water and octanol were measured by ultraviolet-spectroscopy.

Table: 6. Partition Coefficient of drug

Material	Observation
Ondansetron HCl	2.50±0.20

Conformation and authentication of drug

Infrared spectroscopy: -

Infrared spectrum of any compound given information about the functional group present in particular compound. An Infrared spectrum of drug was taken using KBr pellet method. Various peaks in IR spectrum were interpreted for presence of different group in the structure of drug. The IR spectrum was recorded on Shimadzu 8400-S FTIR spectrophotometer Japan and presented in Figure 5.1(B)

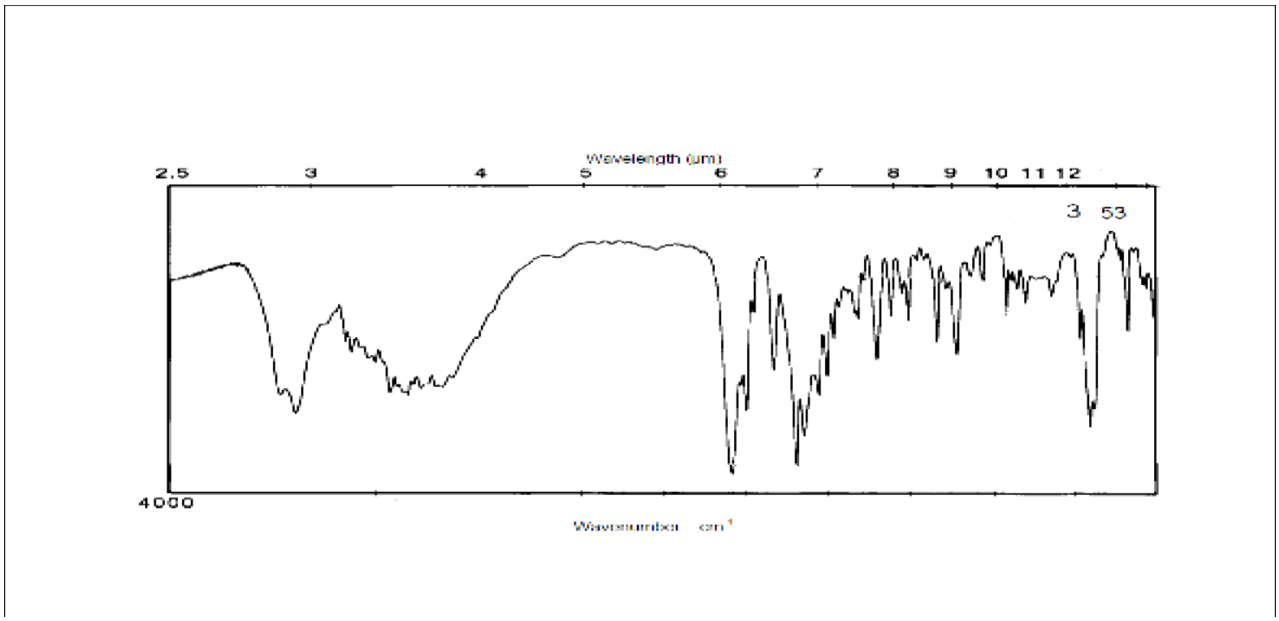

Figure : 1. Standard infrared spectrum of drug sample

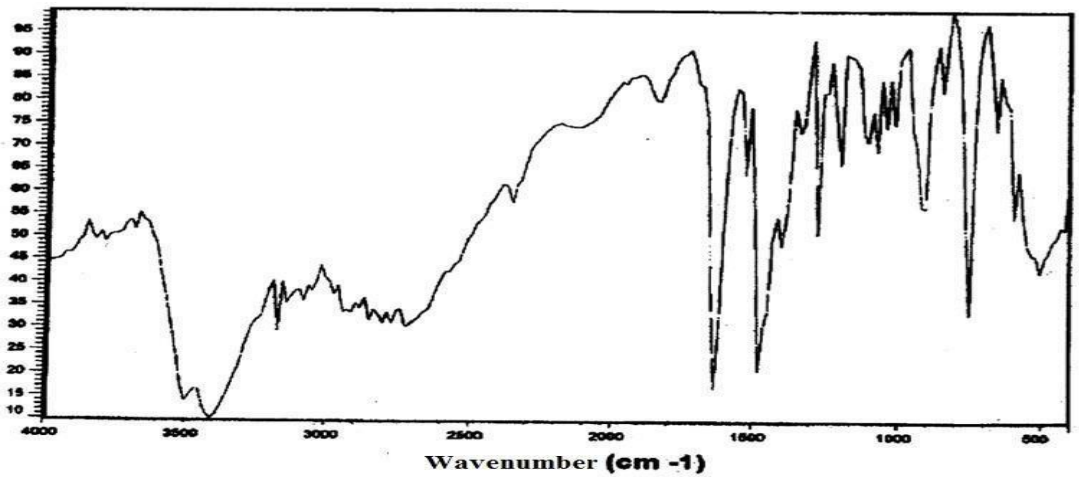

Figure: 2. Infrared spectrum of drug sample

Table: 7 IR Peak of drug sample

Peak Maximum (cm^{-1})	Assingment
756	o- disubstituted benzene
1279	C-N
1458 & 1479	CH_3
1531	C=C aromatic
1638	C=N, C=O ring
3410	H_2O

Ultra-Violet (UV) spectroscopy

Organic molecules when exposed to light in UV region they absorb light of particular wavelength depending on the type of electron transition associated with the absorption. The absorption maximum of drug was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.10 mg of drug was weighed accurately and dissolved in 10 ml of methanol in 10 ml of volumetric flask and suitable stock solution was prepared. The spectrum of this stock solution was run in 200-400 nm range in ultra-visible Spectrophotometer (Shimadzu 1700, Japan).

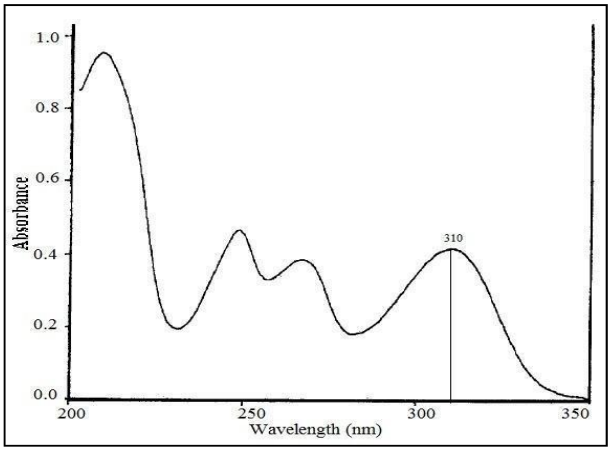

Figure: 3. UV scan of drug in Methanol

Melting Point

It is one of the parameters to judge the purity of crude drugs. In case of pure chemical or photochemical, melting points are very sharp and constant. Since the crude drugs contain the mixed chemicals, they are described with certain range of melting point.

For melting point determination of the drug sample, small quantity of powder was placed into a fusion tube. That tube was placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradually increased automatically and temperature at which powder started to melt was recorded and the temperature when all the powder gets melted was also recorded.

Table: 8. Melting point of drug

Material	Observation
Ondansetron HCl	226-237°C

Quantitative estimation

Calibration curve in methanol

10 mg drug was weighed accurately and transferred to 10 ml volumetric flask. Drug was dissolved in sufficient quantity of methanol and volume upto 10 ml was done with methanol. Thus the stock solution of drug in methanol was prepared.

Preparation of standard calibration curve of Ondansetron HCl drug in methanol

From above stock solution various dilutions were prepared to get concentration, 5-50 µg/ml. The graph of concentration v/s peak area was plotted and data was subjected to linear regression analysis on the maximum absorbance (λ_{max}) 290nm.

Table: 9. Calibration curve of drug in methanol

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.114
3	10	0.210
4	15	0.318
5	20	0.431
6	25	0.510
7	30	0.620
8	35	0.711
9	40	0.826
10	45	0.900
11	50	0.972

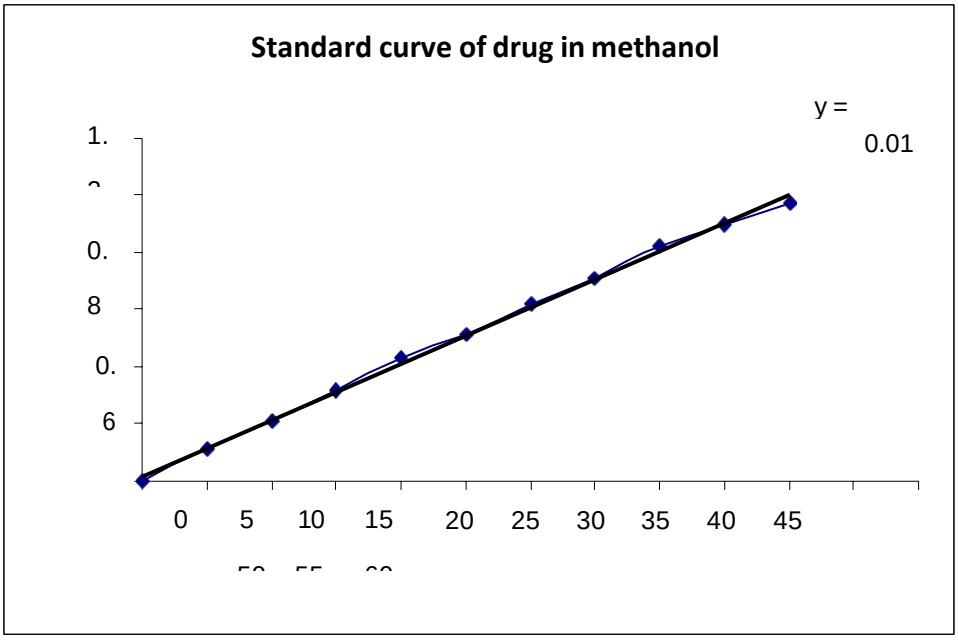

Figure: 4. Standard curve of drug in methanol

Calibration curve in standard phosphate buffer (pH 6.8)

Preparation of the phosphate buffer pH 6.8

Solution A (potassium dihydrogen phosphate solution)

2.72 gm of potassium dihydrogen phosphate was weighed accurately and was dissolved in sufficient quantity of distilled water and further volume upto 100 ml was also done with distilled water.

Solution B (0.2M Sodium hydroxide solution)

0.2 M sodium hydroxide solution was prepared by taking 0.8 gm NaoH and volume upto 100 ml was done with distilled water. Further 50 ml from solution A and 22.4 ml from solution B were taken and mixed and volume upto 200 ml was done with distilled water.

Preparation of standard stock solution

10 mg drug was weighed accurately and transferred to 10 ml volumetric flask. Drug was dissolved in sufficient quantity of standard phosphate buffer pH 6.8 and volume make upto 10 ml with buffer.

Preparation of Standard Calibration curve of Ondansetron HCl in standard phosphate buffer pH 6.8

From above stock solution various dilutions were prepared to get concentration, 2-20 µg/ml. The graph of concentration v/s peak area was plotted and data was subjected to linear regression analysis on the maximum absorbance (λ_{max}) 310 nm.

Table: 10. Calibration curve of drug in standard phosphate buffer (pH 6.8)

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.103
3	4	0.185
4	6	0.282
5	8	0.370
6	10	0.454
7	12	0.541
8	14	0.634
9	16	0.744
10	18	0.841
11	20	0.937

COMPATIBILITY STUDY

Drug Excipients Interaction

Compatibility of the drug with excipients was determined by differential scanning calorimetry (DSC) analysis. This study was carried out to detect any change on chemical constitution of the drug after combination with the excipients in the ration (1:1).

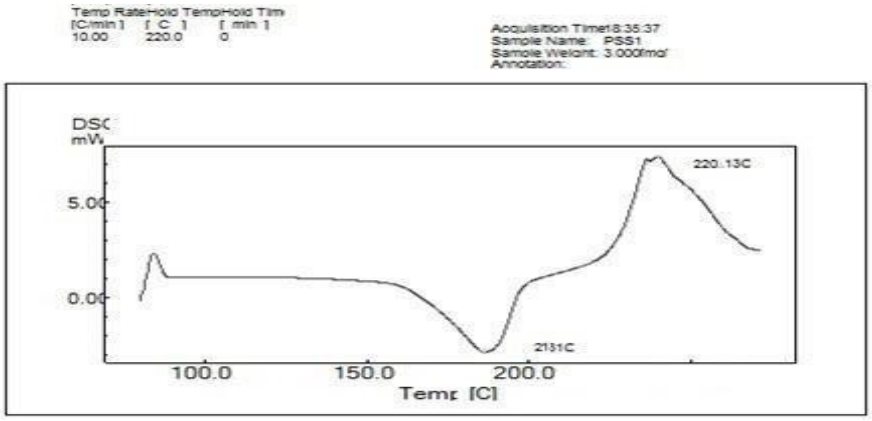

Figure: 5. DSC Thermogram of drug sample

CONCLUSION:

Preformulation testing is the first step in the rational development of dosage forms of a drug substance Preformulation study was done initially and results were directed for the further courseof formulation.

The physical characteristic like organoleptic properties of drug sample was performed and it was found to be bitter in taste, colour was white crystalline powder and was odourless. And hence the drug sample was found to be as per specifications. The quantitative solubility of drug was determined and it was found that drug freely soluble in methanol and ethanol, sparingly soluble in chloroform and slightly soluble in water. And this result indicated that the drug is poorly water soluble and soluble in organic solvents like methanol and ethanol. The partition coefficient of drug was determined as per procedure. It was found to be 2.50 that indicated that the drug was portioning maximum in lipophillic phase and hence it was found that drug was lipophillic in nature. Identification and authentication of drug sample was done by *infrared spectroscopy*. The IR spectra showed the presence of principal groups like at 756 o- disubstituted benzene; 1279 C-N; 1458 & 1479 CH3; 1531 C=C aromatic; 1638 C=N, C=O ring and at 3410 H_2O. The principal groups of infrared spectroscopies showed that the drug sample was authenticated. Identification and authentication of drug sample was done by ultraviolet spectroscopy and it was scanned in the range of 200-400 nm. Drug absorption maximum λ_{max} was found to be at 310 nm. Absorption maximum showed that drug sample was authenticated. Melting point was also determined by melting point apparatus. The melting point was found in the range between 226^0-237^0C which meets as per specification. The melting point showed that drug sample was authenticated.

Quantitative estimation of drug sample was done by different calibration curves which were prepared in methanol, phosphate buffer solution pH 6.8 in concentration range of 5-50 µg/ml and the R^2 value was found to be 0.9979 and 0.9991 respectively which indicated the linearity of the graph. DSC thermogram showed endothermic and exothermic peaks. Drug and polymer displayed their characteristic individual melting trends without any appreciable deviation. From this it is observed that there is no interaction between drug and polymer. particle size. The results of loading efficiency showed that the higher drug loading efficiencies were obtained at the higher drug : polymer ratios.

The relatively high percentage yield and loading efficiency of microballons indicated that the method is suitable for preparing the microballon formulations. Quasi-emulsion solvent diffusion method is simple, less time consuming and involves use of safer ingredients than free radical polymerization and hence more preferred.

All characteristic peaks of microspongic drugs found in FTIR were concordant with spectra of pure drug. DSC studies revealed possible partial amorphization of drugs. SEM images showed that microballons formulation (F6) were finely spherical and uniform.

The microballons differ from regular microspheres with their highly porous surface. This characteristic gives property to release the drug at a faster rate through the pores. Due to smaller pore diameter, the Eudragit Rs 100 microballons showed less and slower drug release in the *in- vitro* release studies. Release from all the microballons followed zero order reaction kinetics.

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