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Formulation Development and Evaluation of Diacerein Loaded Microsphere by Spray Coating (Wurster Method)

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ABSTRACT

Diacerein loaded microspheres were prepared by spray coating(wurster method) using hydroxyl propyl methyl cellulose (HPMC) and ethyl cellulose as release retarding polymer with a view to manufacture sustained release drug delivery. Drug content in the microspheres was determined by HPLC assay followed by drug entrapment efficiency. Shape and Surface topography of Diacerein loaded microspheres was determined by scanning electron microscopy. Fourier transform infrared spectroscopy (.FT-IR), X-ray diffraction Spectroscopy (XRD), and Differential scanning calorimetry (DSC) studies were done to establish drug polymer and other excipients compatibility and stability. Sustained release action was established by In-vitro release study. The result shows that Diacerein loaded microsphere using hydroxyl propyl methyl cellulose and ethyl cellulose polymer can be a new addition in the field of pain management for the treatment of osteoarthritis.

Keywords: Microsphere, Diacerein, HPMC, Ethyl cellulose, Spray coating.

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INTRODUCTION

Nowadays conventional dosage forms of drugs are rapidly being replaced by the new and novel drug delivery systems, among these sustained release or control release dosage forms are very popular in present day therapy. Diacerein or Diacetylrhein comes under the class anthraquinone derivative. Chemically it is 9,10-dihydro-4,5-dihydroxy-9,10-dioxo-2-anthranoic acid diacetate[1]. Diacerein is thought to act via inhibition of interleukin-1Beta, a protein involved in the inflammation and destruction of cartilage that play a role in the development of symptoms of degenerative disease like osteoarthritis. Diacerein is a short acting drug, practically insoluble in water. Oral bioavailability of Diacerein is about 35to56%. Hence, the drug was selected for preparation of sustained release formulation. The study design was to prepare microsphere of Diacerein by spray coating with HPMC and ethyl cellulose as coating polymer which not only provides prolong therapeutic action but also reduce one of its major adverse side effect of Diacerein induced diarrhoea or soft stool and yellow color urine[2-7].

MATERIALS & METHODS

For the present study Diacerein Mfgd by: M/s Elder Pharmaceuticals Ltd., A-36, MIDC, Industrial area, Patalganga, Mumbai was obtained as free gift. HPMC, Ethyl cellulose, MCC were from S. D. fine Chemicals Ltd. All other chemicals were of A. R. grade manufactured by Merk Ltd. and Sigma Aldrich.

Instruments used:-

* Mini Lab Coater, Manufacturer- Umnag Pharmatech Pvt. Ltd
* HPLC – Perkin Elmer (Model Flexar)
* Dissolution apparatus, Make Lab India, model DS 8000+
* IR – Shimadzu (Model Prestige 21)
* Differential scanning Calorimetry (Model DSC 4000, software Pyris)

Manufacturing process of Diacerein Microsphere:-

1st Stage: Preparation of Drug pellet:

Quantity of Dummy pallets taken for coating: - 300.0 gm.(size #18-20)

Coating Solution formula:

Sr. No.	Ingredients	Quantity (%)	Quantity (g)
1.	Diacerein	5.34%	110.0g
2.	HPMC 6 cps	2.43%	50.0g
3.	Isopropyl alcohol (50%)	46.12%	950.0g
4.	Methylene Dichloride (50%)	46.12%	950.0g
	Total:	100.00%	2060.0g

Reconstitution: 7.77% w/w

Procedure:

- Weighed and mixed 110.0 g of Diacerein and 50.0 g of HPMC 6 cps and passed through # 40 mesh.
- Added the above blend to Isopropyl Alcohol under stirring. Added weighed quantity of Methylene dichloride and continued stirring for 45 minutes.
- Passed the above coating solution through #80 muslin cloth.
- Stirring was continued during the entire coating process to avoid settling.

Coating Parameters:

Inlet temperature	40° C
Product Temperature	31-34° C
Exhaust Temperature	28-32°C
Airflow (cfm)	6-8
Drive (%)	45-60
Atomization (bar)	1.5-1.7
Spray pump (rpm)	1.0-4.0
Process pump (rpm)	1.0-4.0
Process time	6 hours

Theoretical Weight gain: 36.67%

Actual Weight gain: 35.00 %

2nd Stage: Modified Release Coating:

Quantity of Drug loaded pellets taken for coating: 405.0 g.

Coating Solution formula:

Sr. No.	Ingredients	Quantity (%)	Quantity (g)
1.	Ethyl Cellulose N7	4.95%	50.0g
2.	Dibutyl Phthalate	0.99%	10.0g
3.	IPA	47.03%	475.0g
4.	MDC	47.03%	475.0g

Reconstitution: 5.94% w/w

Procedure:

- Weighed and mixed 50.0g of Ethyl Cellulose N7 and 10.0g of Dibutyl Phthalate.
- Added the above to Isopropyl alcohol under stirring. Added weighed quantity of Methylene Dichloride and continued stirring for 45 minutes.
- Passed the above coating solution through # 80 mesh muslin cloth.

Coating Parameters:

Inlet temperature	40° C
Product Temperature	31-35° C
Exhaust Temperature	31-32° C
Airflow (cfm)	7-8
Drive (%)	55-65
Atomization (bar)	1.0-1.9
Spray pump (rpm)	1.0-5.0
Process Time	4 hours

Theoretical Weight gain: 14.81%

Actual Weight gain: 13.58 %

Evaluation of Diacerein microsphere

Assay of Diacerein in microsphere by HPLC: The diacerein microsphere was assayed by HPLC following methods as described for assay of Diacerin capsules in IP 2014 monograph. The assay was done on a C18 (15cm) column with Triethyl amine buffer (pH 3.0 with Phosphoric acid) and Acetonitrile in the ratio 75: 25 as mobile phase at a flow rate of 1.0 ml/min with 20 microlitre of load. The column was maintained at 40°C temperature and detection was carried out by UV visible detector at 254 nm. Perkin Elmer HPLC Model Flexar was used in the assay. The microsphere formulation was finely ground in morter pestle and accurately 0.035 g of pellet was taken in triplicate in 3 separate 100 ml volumetric flasks and 70 ml diluents was added. Each solution was sonicated 15 min and volume was made up to the mark. Further 5 ml of each solution was diluted to 10 ml with diluents and these solutions were assayed against Diacerein standard solution of 0.05mg/ml. The average assay was calculated to be 146.17 mg/g of microsphere.

Drug entrapment efficiency was calculated to be 61.08%

In-vitro dissolution rate study of Diacerein microsphere:

In vitro dissolution were performed for Diacerein microsphere using USP type II dissolution test apparatus (Paddle type) at 370C and 50rpm in Phosphate buffer PH 6.8 and citrate buffer 6.0(500ml) dissolution medium. An accurate amount of microsphere (eqv. To 50mg Diacerein) was added to dissolution medium and at preset interval time

of 1,2,4,8,12,16,20,24hrs and 5ml aliquots were withdrawn and replaced by an equal volume of fresh dissolution medium. Aliquots following suitable dilution were analyzed by UV visible spectrophotometer at wavelength 254 nm for phosphate buffer and 340nm for citrate buffer.

Table 1. Dissolution of Diacerein microsphere in Phosphate buffer pH 6.8

Time (hr)	Avg % of Drug Release
1	10.62
2	22.42
4	42.38
8	63.75
12	70.4
16	89.27
20	97.6
24	73.3

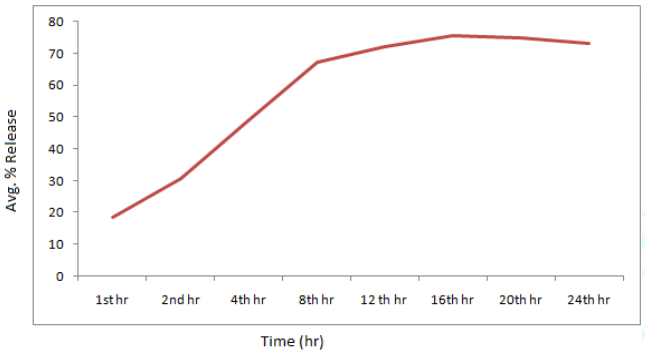

Fig. 1 Dissolution of Diacerein microsphere in phosphate buffer pH 6.8

Table. 2. Dissolution of Diacerein microsphere in Citrate buffer (Table -2)

Time (hr)	Avg % of Drug Release
1	8.28
2	20.01
4	31.89
8	38.58
12	48.09
16	50.12
222 20	56.48
24	57.65

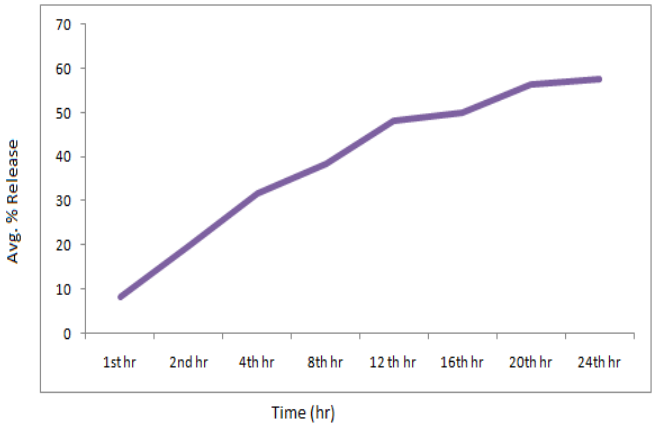

Fig.2. Dissolution of Diacerein microsphere in citrate buffer

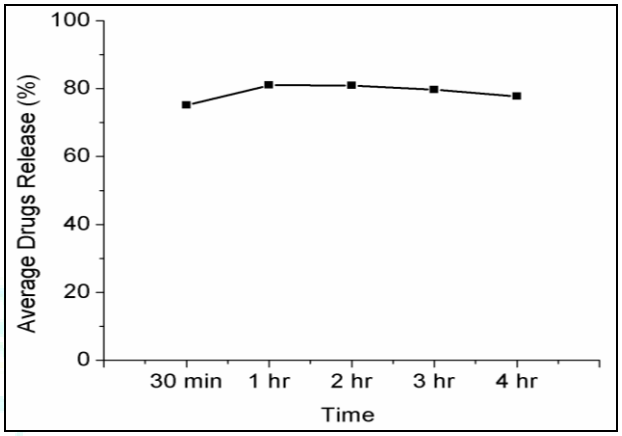

Fig. 3. Dissolution of Diacerein capsule (marketed preparation) in phosphate buffer pH 6.8

Scanning Electron Microscope study of Diacerein loaded microsphere

Scanning Electron Microscope (SEM) studies were carried out by using JEISS make (UK) model (JSM 6360). It was used to characterize the shape and surface topography of the microspheres. Microspheres were mounted on conducting stubs and vacuum coated with gold palladium film using a sputter coater (Edward S – 150, UK). Images were taken using 17kv electron beam intensity in a scanning electron microscope to examine the surface morphology of the microspheres.

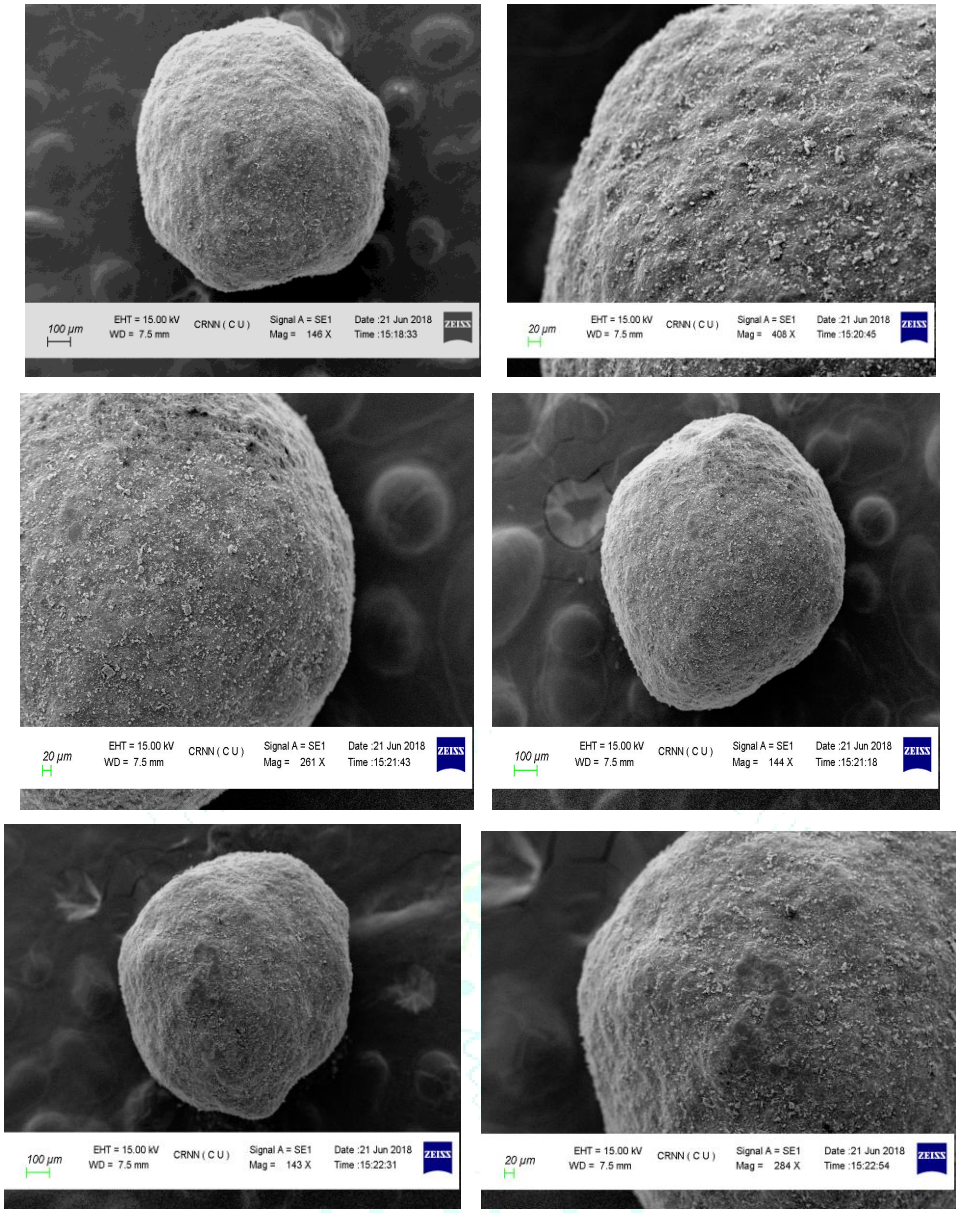

Fig. 4. SEM of Diacerein microsphere

Fourier Transform Infrared Spectroscopy (FT-IR Study):

Drug- polymer interactions were studied by FTIR spectroscopy in Shimadzu Japan (Model no. Prestige-21) Samples were prepared in Kbr dises (2mg sample in 200mg Kbr). FTIR study was performed on Diacerein, Microsphere and physical mixture. The scanning region was from 4000 to 400cm^{-1}.

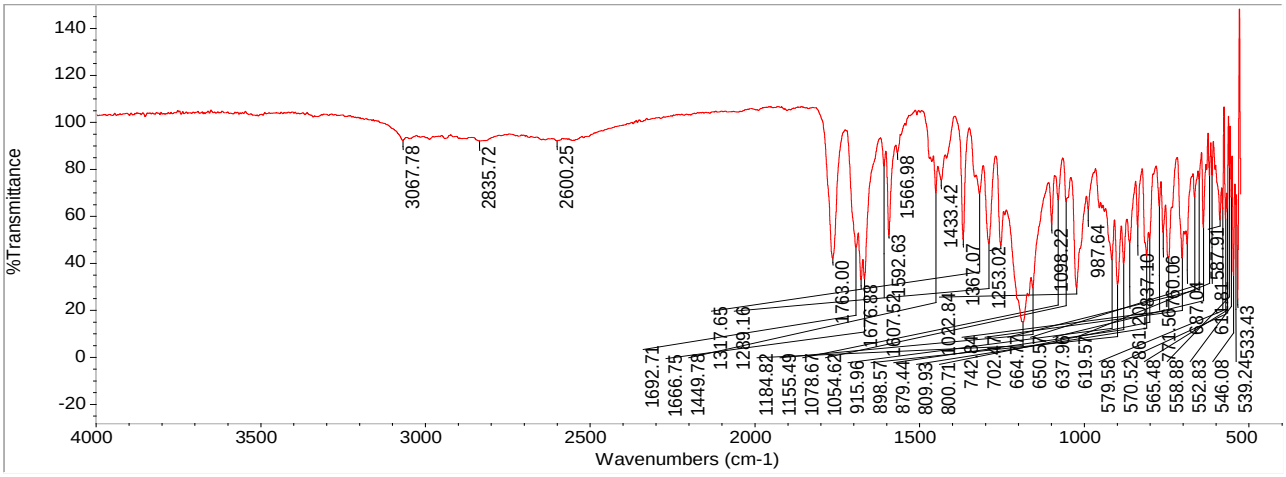

Fig. 5. FTIR, of Diacerein API

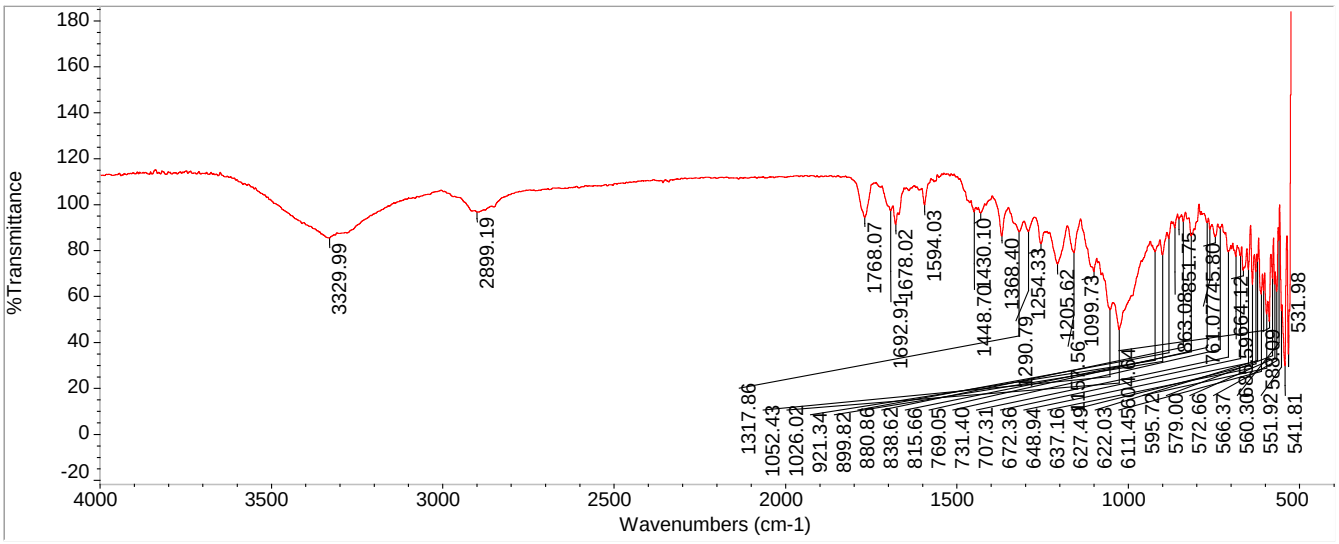

Fig. 6. FTIR of Diacerein Microsphere

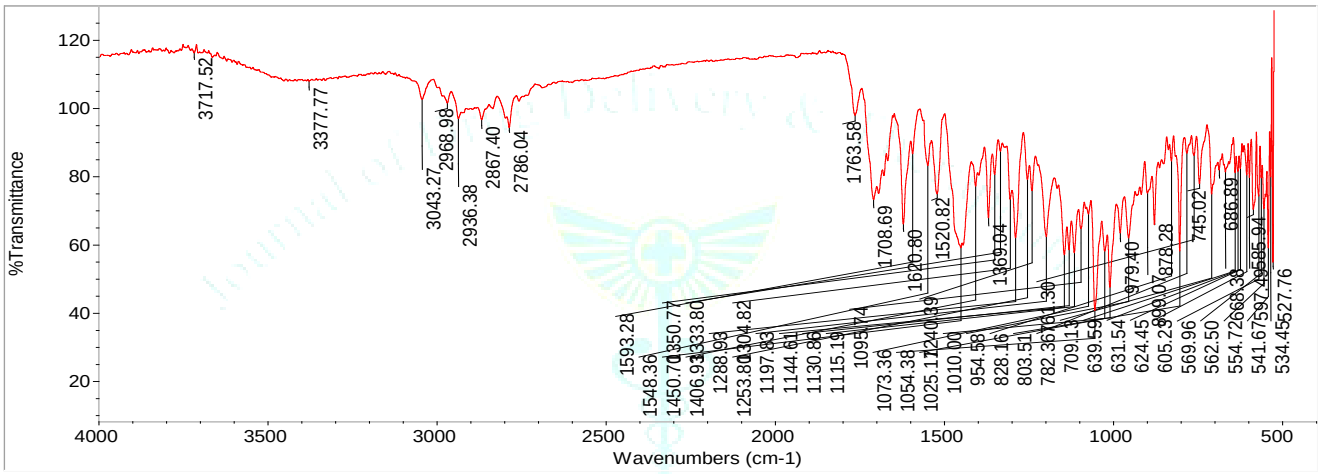

Fig. 7. FTIR of Diacerein with other ingredients physical mixture.

X- Ray Diffraction Analysis:

X-ray diffratometry of Diacerein, Diacerein loaded microsphere, and Physical mixture of Diacerein and other ingredients were done by using MODEL – ULTIMA-III, RIGAKU (MAKE JAPAN), Cu target slit 10mm. The samples were mounted on to the diffractometer and ciliated the X-rays on to the powdered sample to get the diffraction peak of certain intensities and recorded scan speed and scan axis were 1.000deg/min and 20/0 respectively.

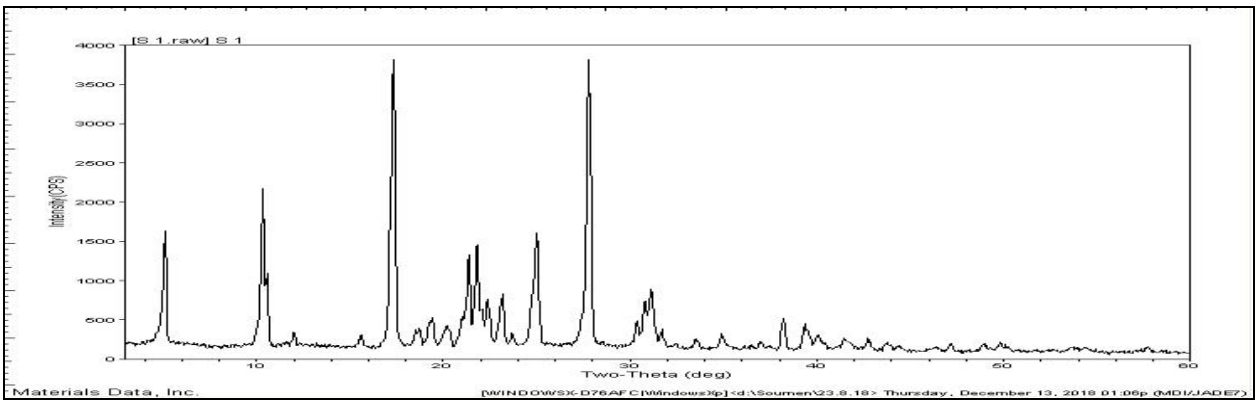

Fig. 8. XRD of Diacerein API

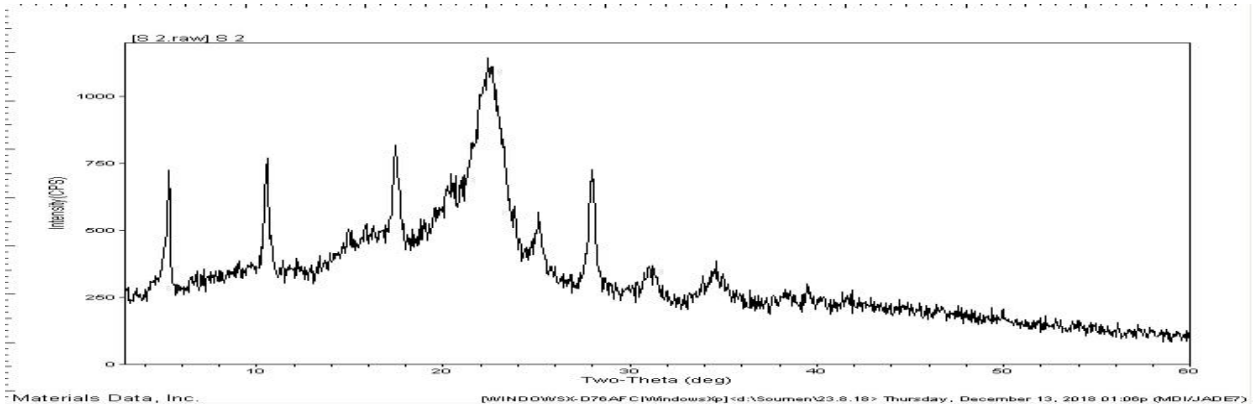

Fig.9. XRD of Diacerein Microsphere

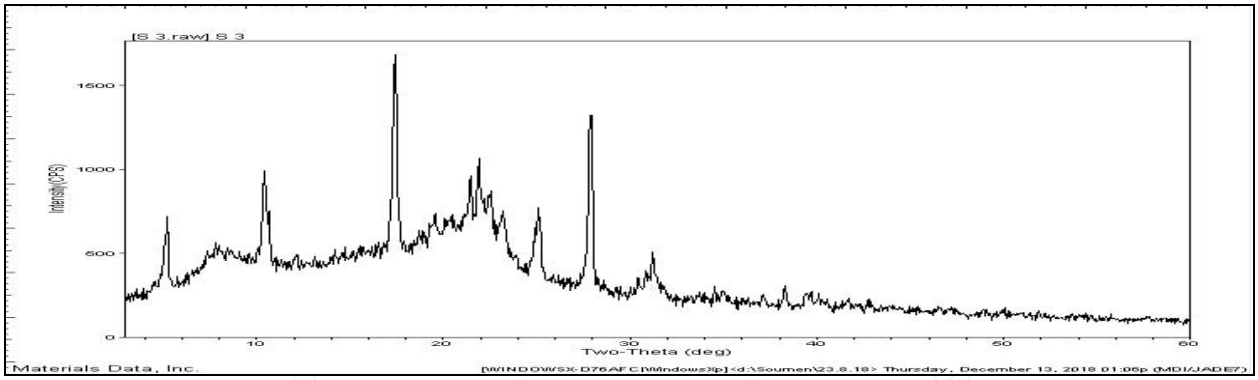

Fig. 10. XRD of Physical Mixture of Diacerein and Ingredients

Differential Scanning Calorimetry:

DSC study of Diacerein API, microsphere and drug and ingredients physical mixture were studied in Perkin Elmer (model DSC 4000), software Pyris. DSC thermo grams were shown in fig 10, 11 &12) which shows drug stability and compatibility during the process.

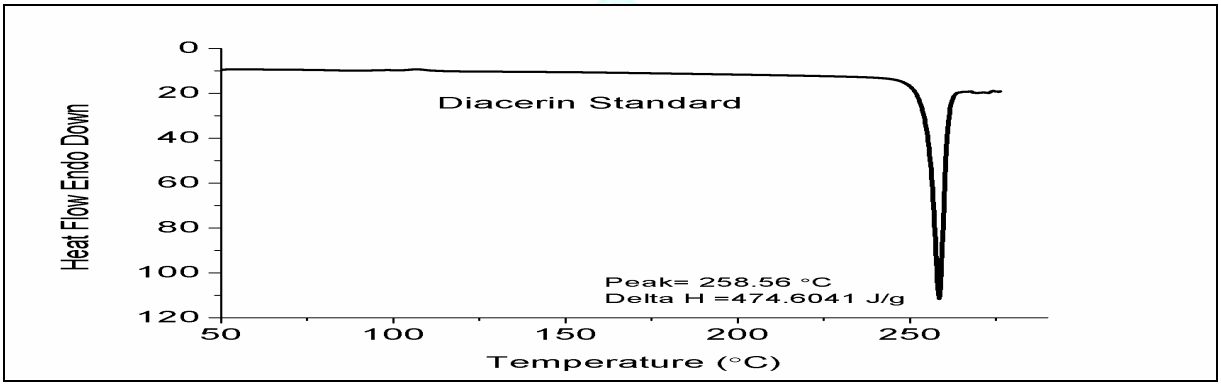

Fig. 10. DSC of Diacerein API

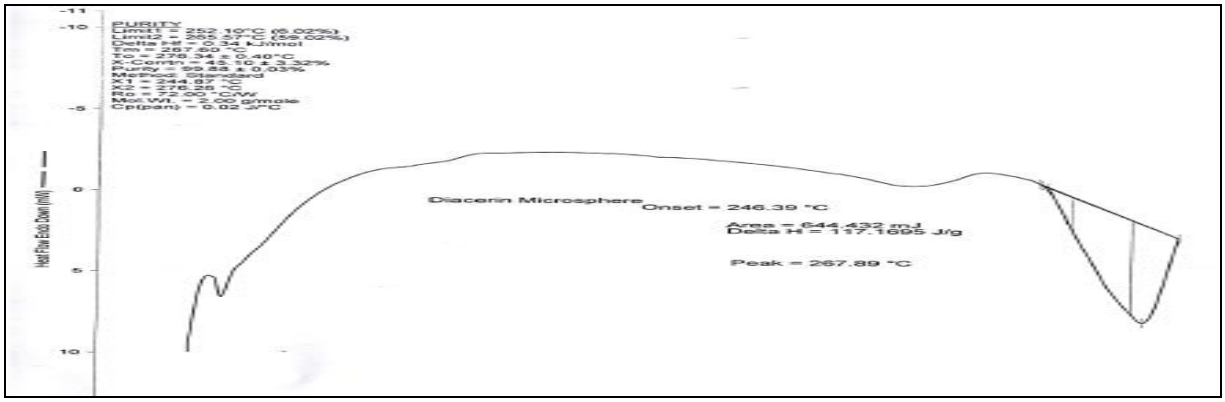

Fig. 11.DSC of Diacerein Microsphere

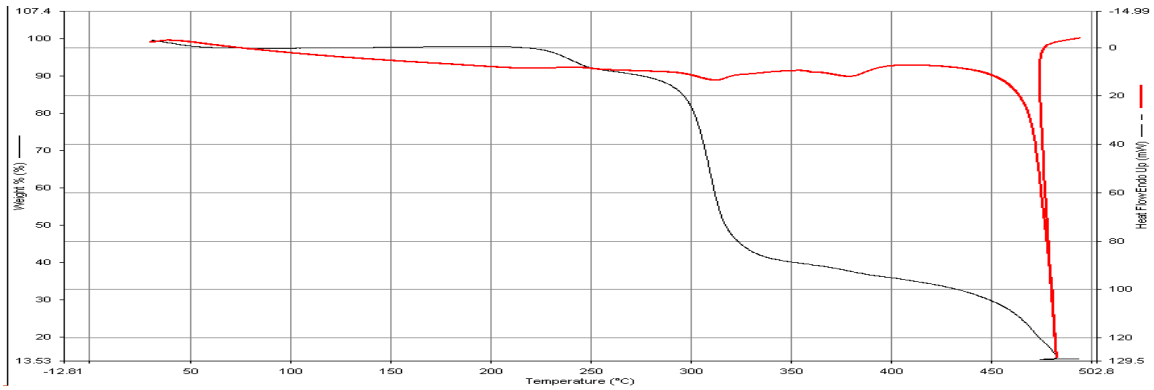

Fig. 12. DSC of Physical Mixture of Diacerein and Ingredients

RESULTS AND DISCUSSION

Scanning Electron Microscope

Scanning electron microscopy (SEM) of drug loaded microsphere of HPMC and ethyl cellulose reveals that the microspheres posses spherical, non-aggregated and porous surface (fig a, to, g) By SEM study it had been seen that the size of the optimized Diacerein loaded microsphere was 20 μm to 100 μm. Magnification of 144, 261, 146 and 408 shows the spherical shape and partially porous nature of the microsphere. The formation of pore may cause solvent to penetrate resulting in the swelling of the internal matrix and release of the drug either burst release or through diffusion. Formation of pore means diffusion mechanism to be responsible for sustained release.

FTIR Study

The FTIR patterns of Diacerein(API), Diacerein microsphere and Diacerein and other ingredients physical mixture are shown in Fig S_4B,S_1B and S_5B.The FT-IR spectra of pure Diacerein showed sharp peak at 1690 cm^{-1} (which may be due to C=O stretching amide), 2937 cm^{-1}(C-H stretching aliphatic) and 1766 cm^{-1}(C=O Stretching ester). The identical peaks also present in Diacerein loaded microsphere and Physical mixture of Diacerein and other ingredients. The result shows drug stability during the process.

X-RAY Diffraction Spectroscopy (XRD)

X-ray diffraction Spectroscopy was done to establish the stability and compatibility of the Diacerein with other excipients when formulated into microsphere. The diffraction pattern of pure drug was compared with Diacerein microsphere and physical mixture of Diacerein with other ingredients used in formulating the microsphere. Since each diffraction pattern is characteristic to a specific crystalline lattice for a given compound, the purity and stability of the drug in the dosage form can be established through it. The X-ray diffraction pattern shows that there is little change in crystalline structure of Diacerein as pure drug, Diacerein microsphere and Physical mixture of Diacerein with other ingredients. Slight shift in Diacerein microsphere and Physical mixture of drug and other ingredients may take place due to reduction of purity of the drug during formulation of microsphere and physical mixture.

Differential Scanning Calorimetry (DSC)

The DSC analysis of Diacerein as pure drug, microsphere and Physical mixture of Diacerein and other ingredients elicited an endothermic peak very close to each other. Thus it was thought to indicate the absence of chemical interaction between the drug and polymer.

In – vitro Drug Release Study

The in-vitro release profile of Diacerein microsphere and Diacerein commercial capsule were compared. The drug release rates from the developed microspheres were significantly retarded when compared with commercially available capsule. Diacerein microspheres showed release retarding effect in both phosphate buffer at pH 6.8 and citrate buffer at pH 6.0.

CONCLUSION

The study confirms that Diacerein loaded microsphere can be prepared using HPMC and ethyl cellulose as release retarding polymers by spray coating method for sustained release drug delivery. Further study needs in vivo correlation.

CONFLICT OF INTERESTS

The authors declares no conflict of interest

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