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## Formulation and evaluation of entacapone sustained release matrix tablets

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### Abstract

The objective of the present investigation was to formulate Entacapone sustained release matrix tablets using various grades of HydroxyPropyl Methyl Cellulose such as K4M, K15M and K100M by the direct compression method. The effect of concentration and viscosity of polymer on *in vitro* drug release and release kinetics was studied extensively including swelling and erosion index. The results of precompression properties of the powder blend were found to be in theoretical range for processing into tablet dosage form. The post compression properties results were found to be uniform within the pharmacopoeial limits. *In vitro* release study exhibited that drug release extended up to 7 h to 18 h. It concludes that an increase in the viscosity of polymer decreased the drug release. The drug release mechanism was observed to follow zero order kinetics and non Fickian diffusion mechanism. Drug-excipient compatibility was characterized by FTIR and DSC study and confirmed that no incompatibility was found.

**Keywords:** Direct Compression, Entacapone, HydroxyPropyl Methyl Cellulose, Parkinsonism, Release Kinetics, Sustained Release tablets.

### 1. Introduction

The short half life of entacapone necessitated for fabricating entacapone sustained release matrix tablets to provide a therapeutic amount of drug and maintain the desired drug concentration i.e. the drug-delivery system should deliver drug at a rate dictated by the needs of the body over a specific period of time. Sustained release tablets are intended to take once or twice daily, when compared with conventional dosage forms that may have to take three or four times daily to achieve the same therapeutic effect. The main advantage in administering a single dose of a drug that is released over an extended period of time to maintain constant or uniform blood level of a drug which often gets translated into better patient compliance, as well as the enhanced clinical efficacy of the drug for its intended use <sup>[1]</sup>.

Oral route has been considered as the oldest and convenient route for the administration of therapeutic agents because of its low cost of therapy and ease of administration <sup>[2]</sup>. One of the best approaches to manufacture sustained release dosage forms is the direct compression of blend of drug, retardant material and additives to formulate a tablet. The drug is embedded in a matrix of the retardant. Alternatively, drug and retardant may be granulated prior to compression <sup>[3-5]</sup>.

Hydroxy Propyl Methyl Cellulose (HPMC) is the most widely used polymers as the gel forming agent in the formulation of sustained release dosage forms. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion are the sequential steps that facilitate the controlled drug release. From these the release rate was mainly controlled by the hydration and swelling properties of HPMC which forms a gel barrier that controls the water penetration and drug diffusion <sup>[6, 7]</sup>. The adjustment of the polymer concentration, the viscosity grade and the addition of different types and levels of excipients of matrix can modify the drug release rate <sup>[8]</sup>.

Parkinsonism is a clinical syndrome characterized by four cardinal features: bradykinesia muscular rigidity, resting tremor and impairment of postural balance, leading to disturbances of gait and falling <sup>[9]</sup>. Parkinsonism is an idiopathic PD, first described by James Parkinson in 1817 as *paralysis agitans*, or the "shaking palsy." The pathological hallmark of PD is a loss of the pigmented, dopaminergic neurons of the substantia nigra pars compacta, with the appearance of intracellular inclusions known as Lewy bodies <sup>[10, 11]</sup>.

Entacapone is a selective, reversible catechol-O-methyl transferase (COMT) inhibitor. It is a member of the class of nitrocatechols.

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The chemical name of entacapone is (2E)-2-cyano-3-(3, 4-dihydroxy-5-nitrophenyl)-N,

N-diethylprop-2-enamide. Entacapone is rapidly absorbed (approx 1 hour) and has an absolute oral bioavailability of 35%.

The principal therapeutic action of the COMT inhibitors is to block this peripheral conversion of levodopa to 3-O-methyl DOPA, increasing both the plasma half-life of levodopa as well as the fraction of the dose that reaches the CNS. Double-blind trials for entacapone has shown to reduce the clinical symptoms of "wearing off" in patients when treated with levodopa/carbidopa [12, 13]. So it usually is given simultaneously with each dose of levodopa/carbidopa. Entacapone has not been associated with hepatotoxicity, which is caused by tolcapone and requires no special monitoring [14, 15, 16].

## 2. Materials

Entacapone was obtained as a gift sample from RA CHEM Labs, Hyderabad. Microcrystalline cellulose was procured from FMC Bio Polymer, usa. HPMC was procured from Colourcon; Asia Pvt LTD. Aerosil was procured from degussa

corp, Germany. Talc was procured from Luzenac corp, Germany. Magnesium stearate was procured from ferro industrial chemicals, usa. All the chemicals used were of analytical grade and purchased from an authorized dealer.

## 3. Method

### 3.1 Formulation Development Of Entacapone Matrix Tablets:

All the matrix tablet formulations were prepared by direct compression method. The formulation development of entacapone matrix tablets was done by using different viscosity grades of HPMC such as K4M, K15M, and K100M at 10%, 12.5%, 15%, 17.5%, 20%. Drug, polymer and excipients were weighed accurately according to the given formula and sifted through sieve No. 30 and mixed thoroughly in a poly bag. The powder blend was compressed using 9.5 mm round concave punches on compression machine (Cadmach Ahmedabad, India).

**Table 1:** Formulation development of Entacapone Matrix Tablets using different viscosity grades of HPMC.

Formulation codes	Ingredients (mg)							
	Entacapone	MCC	HPMC			Aerosil	Talc	Magnesium stearate
			K4M	K15M	K100M			
F1	200	90	35	-----	-----	5	3	2
F2	200	81	44	-----	-----	5	3	2
F3	200	72	53	-----	-----	5	3	2
F4	200	63	62	-----	-----	5	3	2
F5	200	55	70	-----	-----	5	3	2
F6	200	90	-----	35	-----	5	3	2
F7	200	81	-----	44	-----	5	3	2
F8	200	72	-----	53	-----	5	3	2
F9	200	63	-----	62	-----	5	3	2
F10	200	55	-----	70	-----	5	3	2
F11	200	90	-----	-----	35	5	3	2
F12	200	81	-----	-----	44	5	3	2
F13	200	72	-----	-----	53	5	3	2
F14	200	63	-----	-----	62	5	3	2
F15	200	55	-----	-----	70	5	3	2

### 3.2 Bulk properties of powder blend [17]

The prepared powder formulation ready for compression were subjected to measurement of Angle of Repose, Bulk Density, Tapped Density, Carr's Compressibility Index and Hausner Ratio as per the standard procedure suggested.

### 4. Evaluation of matrix tablets

Quality control test like weight variation, hardness, friability were determined as per standard procedure. Weight variation<sup>19</sup> was determined by weighing twenty tablets individually using electronic balance. The test was performed as per IP 2007. Hardness<sup>18</sup> was determined by taking 6 tablets from each formulation using hardness tester (Monsanto hardness tester). Friability<sup>18</sup> was determined by taking 10 tablets from each formulation using Roche Friabilator which was revolved at 25 rpm for 4 mins (Sisco, India). Thickness was measured by using digital vernier callipers (Mitutoyo Corp, Japan) on 5 randomly selected tablets from each formulation.

### 4.1 Uniformity of drug content [19]

Drug content was determined by taking 10 tablets from each

formulation and it was finely powdered. The powder equivalent to 200 mg drug was weighed and dissolved in 100 ml of phosphate buffer pH 5.5. The solution was filtered and 10 ml of filtrate was suitably diluted and absorbance was analysed spectrophotometrically (Labindia UV 3092) at  $\lambda_{\max}$  378 nm against pH 5.5 phosphate buffer as a blank.

### 4.2 Dissolution studies [20, 21]

The release of Entacapone from sustained matrix tablets were determined using USP dissolution testing apparatus II (paddle type) (Labindia DS 8000) at 50 rpm. The dissolution test was performed using 900 ml of pH 5.5 phosphate buffer. The temperature of the dissolution medium is maintained at  $37 \pm 0.5$  °C. 5 ml of the sample was withdrawn at regular intervals and replaced with the same volume of pre-warmed fresh dissolution medium. After filtration, the absorbance of the withdrawn samples was measured spectrophotometrically at  $\lambda_{\max}$  378 nm and the amount of drug release was determined. Dissolution test was carried out until 100% of the drug was released from the formulated tablets. Release studies were conducted in triplicate.

#### 4.3 % Swelling Behaviour of Matrix Tablets <sup>[22]</sup>

The extent of swelling was determined in terms of percentage weight gained by the tablets. One tablet from each formulation was kept in dissolution apparatus USP type I (basket) containing volume of 900 ml phosphate buffer pH 5.5. At the end of 1, 3, 5, 7, 9 h, tablets were withdrawn, soaked on tissue paper and weighed, and then percentage weight gain by the tablet was calculated using the formula.

$$SI = \frac{M_t - M_o}{M_o} \times 100$$

Whereas,

SI = Swelling index,  $M_t$  = Weight of tablet at time 't' and  $M_o$  = Weight of tablet at time '0'.

#### 4.4 % Erosion index of Matrix Tablets

The extent of erosion was determined in terms of percentage weight lost by the tablets. One tablet from each formulation was kept in dissolution apparatus USP type I (basket) containing volume of 900 ml phosphate buffer pH 5.5. At the end of 1, 3, 5, 7, 9 h, tablets were withdrawn, soaked on tissue paper and dried in hot air oven. The dry weight was noted. The % erosion index was calculated using formula.

$$EI = \frac{W_o - W_t}{W_o} \times 100$$

Whereas,

EI = erosion index,  $W_t$  = Weight of tablet at time 't' and  $W_o$  = Weight of tablet at time '0'.

#### 4.5 *In vitro* Drug release kinetics <sup>[23]</sup>:

The rate and release mechanism of drug (entacapone) from SR tablets were analysed by following kinetic models, Zero-Order Kinetics, First order kinetics, Higuchi Model, Hixson Crowell cube root law, Korsmayer Peppas equations.

### 5. Characterization of drug and excipients <sup>[24]</sup>

#### 5.1 Fourier transform infrared (FTIR)

FTIR studies are very helpful in the evaluation of drug-polymer interaction studies. If there is any incompatibility between the drugs and excipients, these can be predicted by changes in the functional peaks (characteristic wave numbers). Diffuse reflectance technique was used (400 to 4000  $\text{cm}^{-1}$ ), drug and various polymers were thoroughly mixed with 300 mg of potassium bromide, compressed and the spectrum was obtained by placing the thin pellet in the light path.

#### 5.2 Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. The instrument is very versatile used to evaluate melting point, enthalpy changes and glass transition temperatures of drug with excipients and polymers. Entacapone was mixed with the excipients and the DSC analysis of each sample under the analogous conditions of temperature range 40 – 300 °C, heating rate 10 °C/min, nitrogen atmosphere (20ml/min) and alumina as reference. Differential Scanning Calorimetry (DSC) was performed on pure drug, composition of the final formulation. DSC measurements were done on a Shimadzu DSC-60 and samples were heated at the rate of 10 °C min<sup>-1</sup>. The samples

were heated in an aluminium cup up to 300 °C.

### 6. Results and Discussion

In the present study, entacapone matrix tablets were prepared by using different viscosity grades of HPMC (k4m, k15m, k100m) at 10%, 12.5 %, 15%, 17.5%, 20% as a drug retardant polymer. A total number of 15 formulations were prepared by direct compression technique.

#### 6.1 Precompression properties of powder blend

The powdered blend of formulations prepared with different viscosity grades of HPMC were evaluated for Bulk properties like the angle of repose, bulk density (BD), tapped density (TD), Carr's compressibility index, and Hausner's ratio. The angles of repose of the entire blend for all the formulations were found to be in the range 25° 46'' ± 1.05 to 29° 69'' ± 1.01. The Bulk Density and Tapped Density ranged from 0.319 ± 0.09 to 0.389 ± 0.03 and 0.412 ± 0.06 to 0.0.499 ± 0.08 respectively. The percent Compressibility index founded between 20.71 ± 1.03 to 25 ± 1.02. The Hauser ratio ranged from 1.26 ± 0.07 to 1.34 ± 0.04. The results were found to be within the theoretical range for processing the blend into tablet dosage form.

#### 6.2 Evaluation of prepared matrix tablets

All the batches were prepared under similar conditions to avoid processing variables. Entacapone sustained release matrix tablets were prepared with HPMC K4M, k15m and k100m. All the formulations passed the weight variation test as per the pharmacopoeial limits. The measured hardness of tablets of each batch ranged 4.2 ± 0.79 to 4.8 ± 0.82 kg/cm<sup>2</sup> which indicates good mechanical stability. Tablets mean thickness were found to be in the range of 4.97 ± 0.07 mm to 5.22 ± 0.08 mm. Friability of each batch was found to be in the range of 0.23% to 0.77%, which ensure that loss of material from the edges of tablets was within the acceptable limits. The % drug content of all the formulations was found to be in the range of 97.56% to 99.75% respectively.

#### 6.3 *In vitro* Drug Release of Entacapone Matrix Tablets

The release rate of Entacapone from sustained matrix tablets were determined using USP dissolution testing apparatus II (paddle type) at 50 rpm using pH 5.5 phosphate buffer. Entacapone (200 mg) sustained release matrix tablets were prepared with HPMC K4M (F1- F5), k15m (F6- F10) and k100m (F11- F15) at 10%, 12.5%, 15%, 17.5% and 20% by the direct compression method. The release of Entacapone mainly depends upon the polymer concentration. In *in vitro* Drug release of Entacapone from the formulations F1 to F5 ranged from 30.21 to 14.21% during the first hour while after 5 h, it was between 71.87 and 45.13%. Burst release was observed on the 1st hour only in formulations containing low polymer concentration which was due to the surface erosion of the polymer. Formulations F1, F2 and F3 showed the complete drug release within 7h, 9h and 10 h respectively. The drug release from formulations F4 and F5 extended up to 12 h and 13h containing a high polymer concentration. Drug release of Entacapone from the formulations F6 to F10 ranged from 26.66 to 10.44% during the first hour, while after 5 h, it was between 67.54 and 38.42%. Formulations F6 and F7 showed the complete drug release within 9 and 12 h respectively. The drug release from formulations F8, F9 and F10 extended up to 13 h, 14 h and 15 h containing a high polymer concentration. It was found that the release rate of the drug from the tablets was

found to decrease with increase in polymer concentration. Drug release of Entacapone from the formulations F11 to F15 ranged from 23.34 to 7.66% during the first hour while after 8 h, it was between 82.1 to 42.98%. Burst effect was observed on the 1st hour only in formulations F11 containing low polymer concentration. Formulations F11 and F12 showed the complete drug release within 11 and 13 h respectively. The drug release from formulations F13, F14 and F15 extended up to 15 h, 16 h and 18 h a containing high polymer concentration.

**6.4 In vitro release kinetics**

The best fit with highest correlation coefficient was found with the zero order model for all the formulations in the range of 0.991 to 0.998 which indicates that the amount of drug release is proportional to the time. To explore the release mechanism *in vitro* dissolution data of all formulations was fitted into the Krosmeier peppas equation. The results showed that most of the release exponent ‘n’ values fell between 0.595 to 0.847. Therefore, it can be inferred that the drug release may have followed anomalous or non-Fickian diffusion.

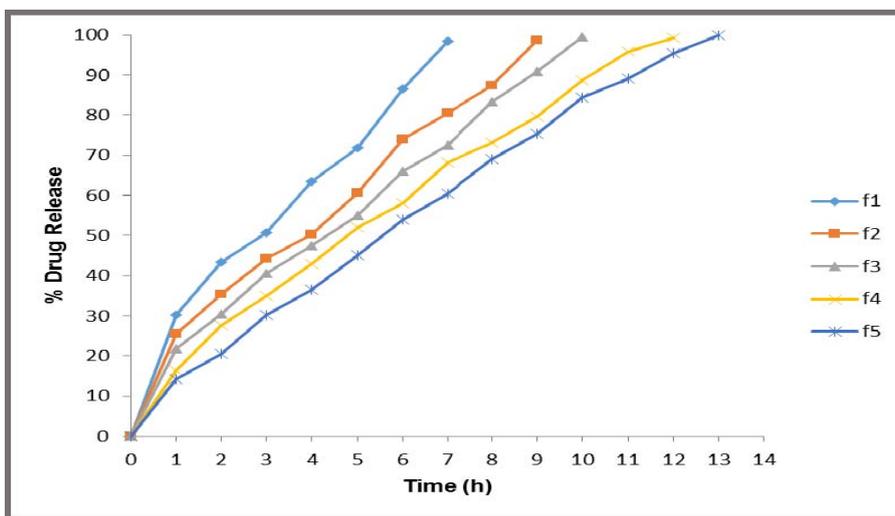
**6.5 % Swelling Index**

The matrix tablets when exposed to dissolution medium, the

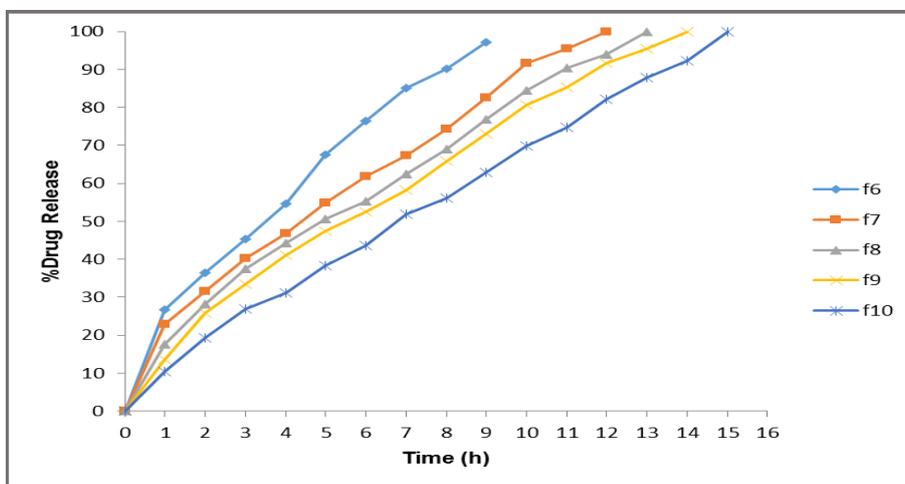
tablet surface becomes wet and started to hydrate to form a viscous gel layer. It was observed that most of the tablets swelled within the six hours for all the 15 formulations and showed good swelling behaviour even up to 9h indicating the greatest water absorption. It was found that the % swelling index increased as the polymer concentration and viscosity was increased. All the batches achieved a very good swelling index that correlates to the drug release mechanism. Maximum swelling was observed to be 205.96% with 20% HPMC K100M and least 92.19% with 10% HPMC K4M

**6.6 % Erosion index**

All the batches achieved good erosion index that correlates to the drug release mechanism. It was observed that Erosion was rapid in the formulations containing low polymer concentration and was slow in the formulation with high concentration and viscosity. Maximum erosion of 61% occurred in formulation 10% HPMC K4M and least of 39% in 20% HPMC K100M at the end of 9 h. Swelling and erosion of the polymer occurs simultaneously. This behaviour is responsible for maintaining zero order release. The results concluded that surface erosion occurred in the tablet formulations.



**Fig 1:** *In vitro* Drug Release profile of entacapone matrix tablets prepared with HPMC K4M



**Fig 2:** *In vitro* Drug Release profile of entacapone matrix tablets prepared with HPMC K15M

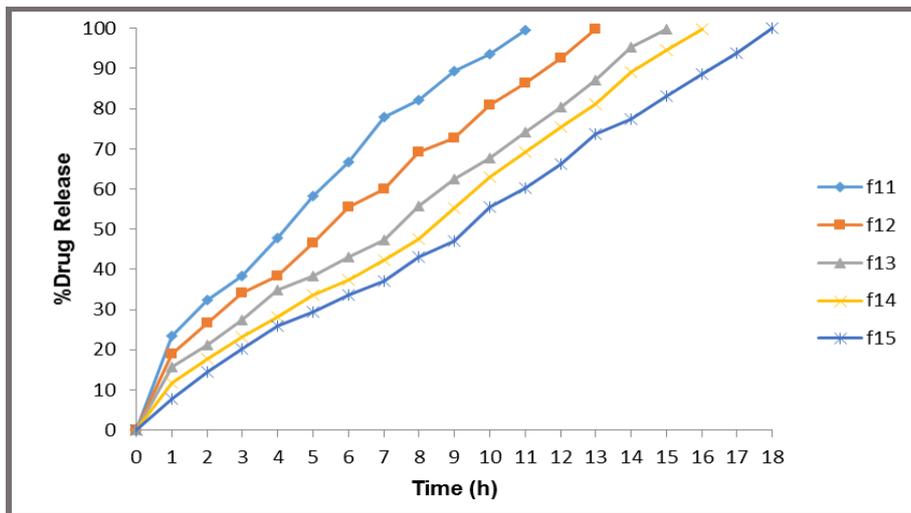


Fig 3: *In vitro* Drug Release profile of entacapone matrix tablets prepared with HPMC K100M

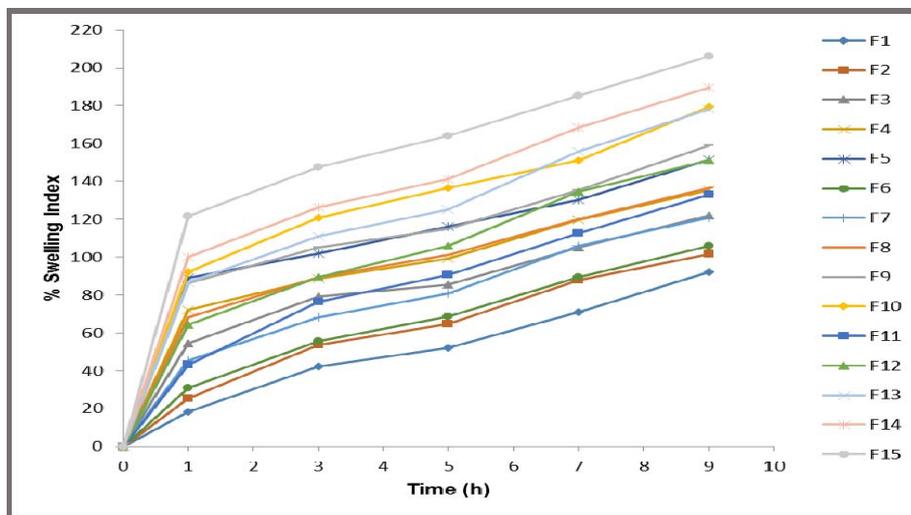


Fig 4: % swelling index of entacapone matrix tablets prepared with different viscosity grades of HPMC

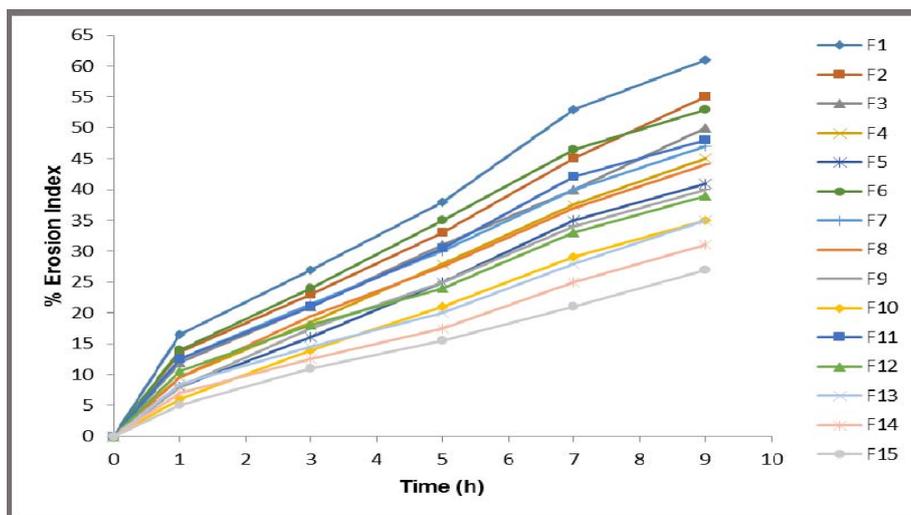


Fig 5: % Erosion index of Entacapone matrix tablets prepared with different viscosity grades of HPMC

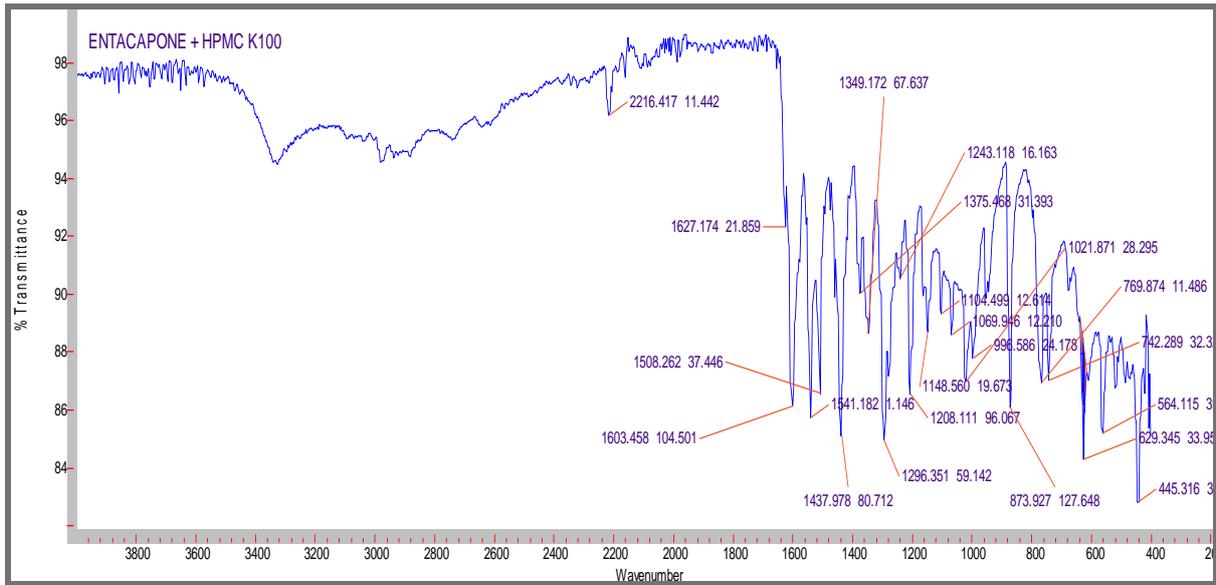
6.7 Fourier Transform Infrared (FT-IR) analysis

FTIR study was conducted on the selected formulations

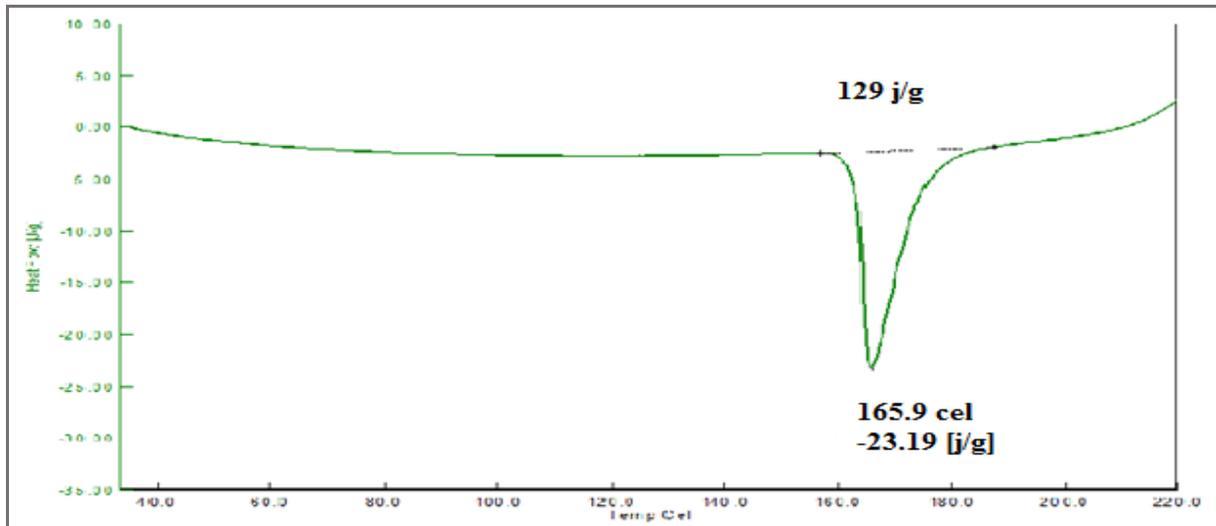
prepared with polymers such as HPMC K4M, K15M and K 100M. Entacapone showed major peaks at O-H stretch =



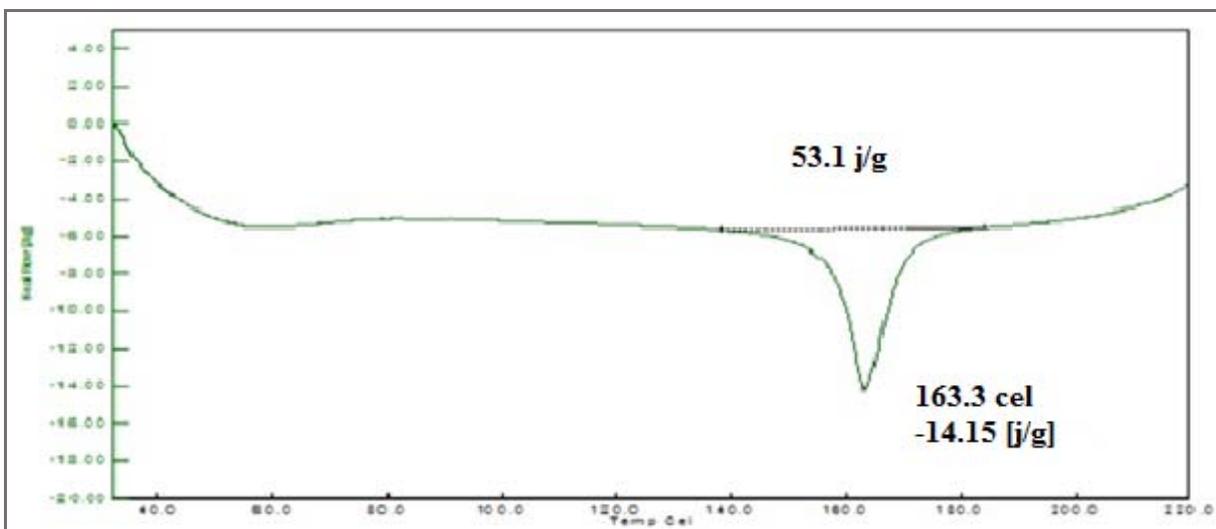
**Fig 8:** FTIR spectral of Entacapone matrix tablets prepared with HPMC K15M



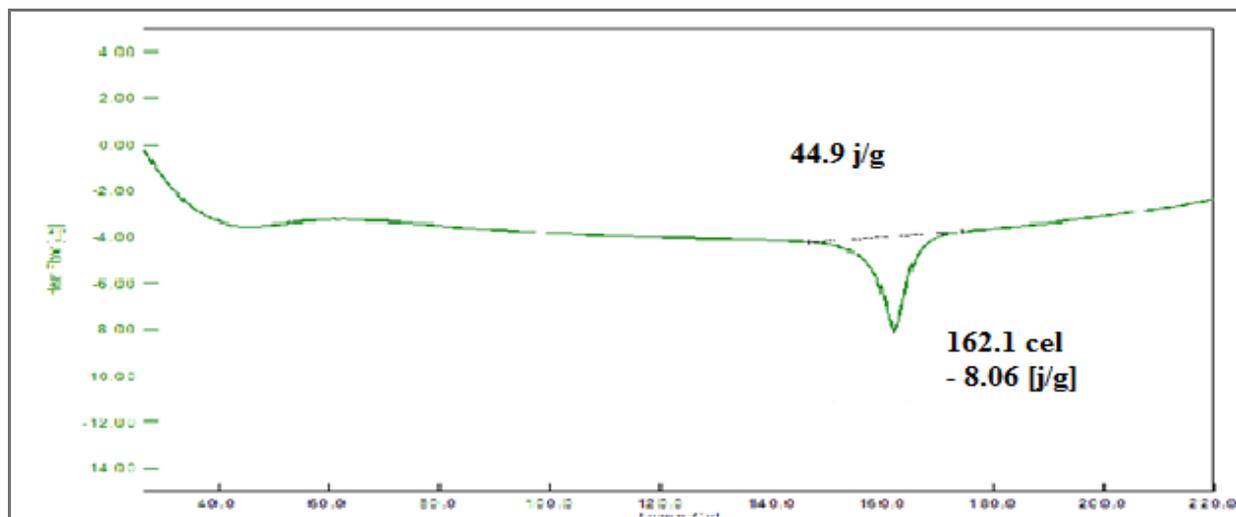
**Fig 9:** FTIR spectra of Entacapone matrix tablets prepared with HPMC K100M.



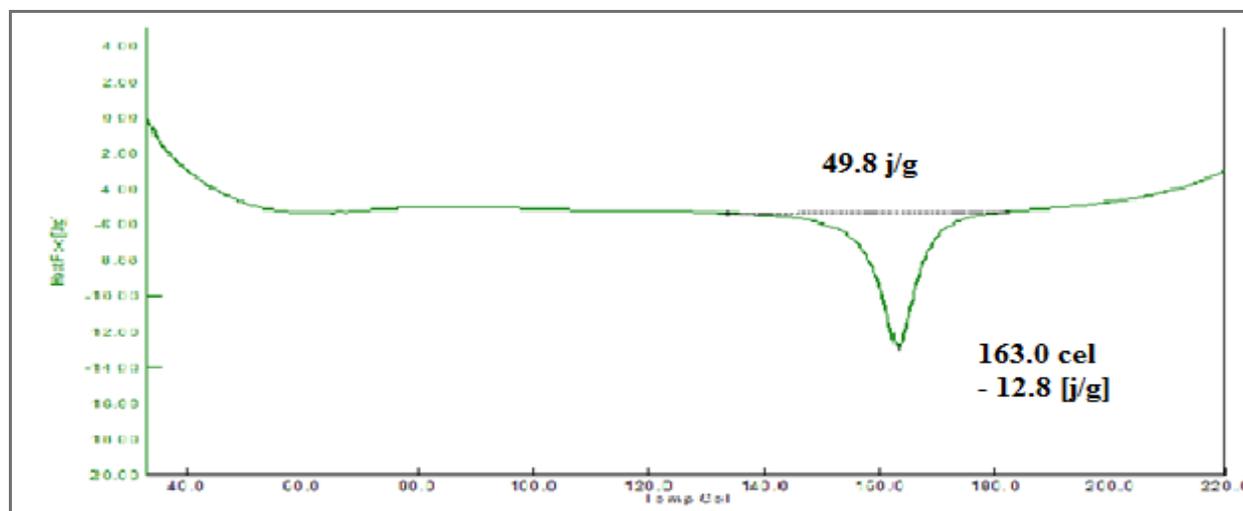
**Fig 10:** DSC thermogram of Pure Entacapone.



**Fig 11:** DSC thermogram of Entacapone matrix tablets prepared with HPMC K4M.



**Fig 12:** DSC thermogram of Entacapone matrix tablets prepared with HPMC K15M.



**Fig 13:** DSC thermogram of Entacapone matrix tablets prepared with HPMC K100M.

### 6.8 Differential scanning calorimetry (DSC)

DSC studies were performed for testing the compatibility between Entacapone, HPMC K4M, K15M and K100M. The pure entacapone showed a sharp endothermic peak at 165.9 °C. Similar endothermic peaks were observed at a similar temperature in the prepared tablets at 163.3 °C with HPMC K4M, 162.1 °C with HPMC K15M and 163.0 °C with HPMC K100M. There was negligible change in the melting point of the physical mixtures and peaks also indicate that entacapone does not form complex with polymer used in the study. Thus, compatibility studies proved that entacapone is compatible with polymer used in the study.

### 7. Conclusion

The present investigation was concerned with the development of entacapone sustained release matrix tablets, using different viscosity grades of HPMC (K4M, K15M, K100M) by the direct compression method. Results of Bulk properties of powder blend were found to be within the theoretical range for processing the blend into tablet dosage form. Quality control test revealed that the results were within the acceptable limits

facilitating the direct compression method for formulating the tablet. *In vitro* drug release results of the study demonstrated that HPMC could sustain the release of entacapone up to 18 h. This may in turn reduce the dosing frequency, thereby improving patient compliance.

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