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DEVELOPMENT AND CHARACTERIZATION OF ENTACAPONE SUSTAINED RELEASE MATRIX TABLETS BY USING THE POLYMER HPMC K4M

MEESA. RAJENDAR, BEEDHA. SARAWATHI, KONDA. MAYURI, AMPATI SRINIVAS

Assistant Professors in St. John College of Pharmacy, Pharmaceutics.

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Abstract: Sustained release has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. Because of increased complication and expense involved in marketing of new drug entities has focused greater attention on development of sustained release or controlled release drug delivery systems Entacapone. The Pre compression powder blend of all the15 formulations was characterized for Flowability and compressibility and results were found to be in theoretical range for processing into tablet dosage form. The prepared tablets of the 5 formulations were characterized for weight variation, hardness, thickness, friability, % drug content and results were found to be uniform within the pharmacopoeial limits. *In vitro* release study exhibited that, in formulations F1 to F5 prepared with HPMC K4M, drug release extended up to 7h to 12h. The release kinetics study shows that drug release followed zero order model for all the formulations which indicates that the amount of drug release is proportional to the time. The Korsmeyer peppas results showed that release follows anomalous or non-Fickian diffusion. It has been shown that in the formulated tablets, swelling and erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug-release rate. FTIR and DSC characterization showed that there is no drug-polymer interaction.

Keywords: Sustained release, HPMC K4M, Entacapone, Evaluation studies of the sustained release tablets

Corresponding Author: MS. MEESA RAJENDAR

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INTRODUCTION

Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose is that the drug is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

Modified release delivery systems may be divided in to 4 categories.

- Delayed Release
- Sustained release
- Controlled Release

- Extended Release
- Site specific targeting
- Receptor targeting

Therapeutic advantages of the SR forms

- Frequency of administration is reduced.
- Patient compliance can be improved.
- Blood level oscillation characteristic of multiple dosing of conventional dosage form is reduced because a more even blood level is maintained.
- Total amount of drug administered can be reduced, thus maximizing availabilit y with minimum dose.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced by formulation in extended action form.
- The safety margin of high potency drug can be increased and incidences of both

local and systemic adverse side effects can be reduced in sensitive patients.

- **Disadvantages of SR dosage form**

Administration of SR dosage form dose not permits the prompt termination therapy.

- Physicians have less flexibility in adjusting dosage regimens. This is fixed by the dosage form regimen.
- SR forms are designed for normal population i.e. on the basis of average drug biologic half-lives. Consequently, disease states that alter drug disposition
- significant patient variation is not accommodated.

MATERIALS AND METHODS

Materials

Entacapone is the gifted sample from the RA KEM Labs, Hyderabad, Microcrystalline cellulose is obtained from the FMC Bio Polymer, usa, HPMC K4M is the procured sample from Color con,

Asia Pvt LTD, Aerosil and Talc are obtained from degussa corp, germany, Magnesium stearate is obtained from ferro industrial chemicals, usa.

Methods

Procedure for preparation of Entacapone matrix tablets:

All the matrix tablets contain 200 mg of API (Entacapone), were prepared by direct compression using microcrystalline cellulose.

Drug, polymer and diluent were weighed accurately according to the formula and mixed in geometric proportions using a mortar and pestle. The mixture was passed through sieve no 40, and thoroughly mixed in a poly bag for 15 mins. The powder blend was then lubricated with Aerosil, talc and magnesium stearate for 5 mins. Finally the powdered blend was compressed into tablets on a 16 station rotary punching machine with 9.5 mm round concave punches.

The Drug -Polymer ratio was developed to adjust drug release as per theoretical release profile. Polymer used was HPMC with three grades K4M with different polymer concentrations are 10%, 12.5%, 15%, 17.5%, 20%. Diluents microcrystalline cellulose was used in preparation of matrix tablets to facilitate direct compression.

Formulation development of Entacapone matrix tablets:

The formulation development of Entacapone matrix tablets was done using different viscosity grade of HPMC such as K4M. MCC was used as diluent, talc and aerosol as anti adherant and glidants, magnesium stearate was used as lubricant.

Formulation development Entacapone matrix tablets with HPMC K4M:

The formulation development was initially done by taking HPMC K4M as shown in table-1. The tablets were prepared at different polymer concentrations such as 10%, 12.5%, 15%, 17.5 % and 20% with the polymer to that of total tablet weight. The tablets were prepared by direct compression method.

The drug, MCC and HPMC K4M were weighed accurately according to the given formula and sifted through sieve no. 40 and mixed thoroughly in a poly bag. Then the above blend was lubricated with aerosol, talc and magnesium stearate as per the formula.

The powder blend was compressed using 16 station rotary compression machine using 9.5 mm round concave shaped punches. The tablets were evaluated for various physico chemical properties and subjected to evaluation parameters.

Table-1: Formulation composition of Entacapone matrix tablets using HPMC K4M.

Ingredients	Formulations				
	F1 (10%)	F2 (12.5%)	F3 (15%)	F4 (17.5%)	F5 (20%)
Entacapone	200	200	200	200	200
Micro crystalline cellulose	90	81.25	72.5	63.75	55
Hypermellose	35	43.75	52.50	61.25	70
Aerosil	5	5	5	5	5
Talc	3	3	3	3	3
Magnesium sterate	2	2	2	2	2
Total	335 mg	335 mg	335 mg	335 mg	335 mg

RESULTS AND DISCUSSION:

Ultraviolet spectroscopy:

The calibration curve for Entacapone was done by using phosphate buffer pH 5.5 as shown in table-2 and figure-1. The graph has shown good linearity with R2 value 0.999 in phosphate buffer pH 5.5 which suggest that Entacapone obeys Beer-Lambert Law in the prepared concentrations.

Table-2: Absorbance of Entacapone in pH 5.5 Phosphate buffer.

Concentration (µg/ml)	Absorbance (nm)
0	0
2	0.168
4	0.33
6	0.48
8	0.62
10	0.801

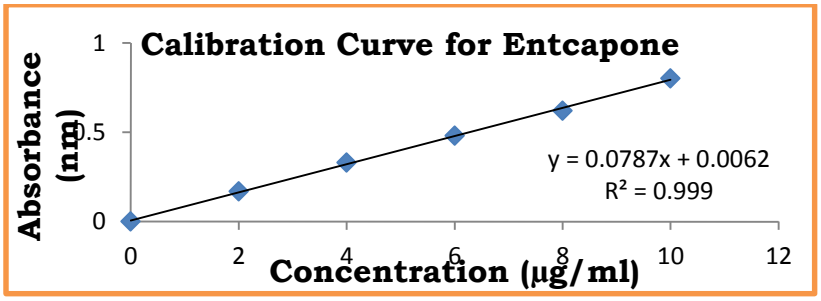

Figure-1: Calibration Curve for Entacapone.

Bulk properties of Entacapone Powder blend prepared with HPMC K4M:

The powdered blend of different formulations was evaluated for bulk properties like angle of repose, bulk density (BD), tapped density (TD), compressibility index, and Hausner's ratio as shown in table-3. The results for the formulated blend were shown in the (Table no 6.3). The angle of repose of the entire blend for all the formulations were found to be in the range 25^0 64'' ±1.04to 28^0 30" ±1.02. Bulk and tapped densities are used for the measurement of Compressibility index and Hausner's ratio. The BD and TD ranged from 0.319±0.09 to 0.381±0.04 and 0.412±0.06 to 0.484±0.07 respectively. Compressibility index was found between 20.71±1.03to 24.15±1.02. The Hauser ratio ranged from 1.26±0.07 to 1.31±0.08. The above results conclude that the powder blend showed good flow properties and were within the Pharmacopeial limits.

Table-3: Bulk properties of Entacapone matrix tablets prepared with HPMC K4M.

Parameters	Formulations				
	F1	F2	F3	F4	F5
Angle of repose	25.64±1.04	25.80±1.09	26.78±1.03	27.29±1.07	28.30±1.02
Bulk density	0.356±0.05	0.381 ±0.04	0.351±0.07	0.319±0.09	0.361±0.02
Tapped density	0.449±0.04	0.484 ±0.07	0.452±0.08	0.412±0.06	0.476±0.03

Carr's index	20.71±1.03	21.28±1.06	22.34±1.04	22.57±1.08	24.15±1.02
Hausner's ratio	1.26±0.07	1.27±0.04	1.28±0.05	1.29±0.03	1.31±0.08

Physical characterization of Entacapone matrix tablets prepared with HPMC K4M.

The compressed tablets of different formulations were evaluated for post compression parameters like weight variation, hardness, thickness, friability, % drug content as shown in figure-4. All the formulated tablets of the formulations F1 to F5 passed weight variation test as per the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets of each batch ranged between 4.2±0.79 to 4.6±0.51 kg/cm^2. Tablets mean thickness were uniform in F1 to F5 formulations and were found to be in the range of 5.02±0.07 mm to 5.21±0.04 mm. The value of % Friability of each batch was found to be in the range of 0.35 % to 0.72%. All formulations showed less than 1% (w/w) friability that indicates the ability of tablets to withstand shocks which may be encountered during transport. % Drug content of all the formulations F1 to F5 were uniform and were found to be in the range of 97.64% to 99.25%. All the tablets conformed to the requirement of assay, as per I.P.

Table-4: Physical characterization of Entacapone matrix tablets prepared with HPMC K4M.

Parameters	**Formulations**				
	F1	**F2**	**F3**	**F4**	**F5**
Weight Variation	335.2±1.62	335.9±1.28	335.5±1.54	335.2±1.46	335.4±1.16
Hardness	4.5±0.82	4.4±0.61	4.2±0.79	4.6±0.51	4.5±0.67
Thickness	5.10±0.04	5.18±0.05	5.21±0.04	5.02±0.07	5.10±0.06
Friability	0.59 %	0.65 %	0.72 %	0.35 %	0.41 %
% Drug Content	98.12	98.75	99.25	99.00	97.64

***In vitro* Drug Release of Entacapone matrix tablets prepared with HPMC K4M:**

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 sustained release tablets were prepared by using HPMC polymers. The in vitro drug release profiles of all the formulations F1 to F5 have been shown in the table 6.5. The release of Entacapone mainly depends upon the polymer concentration. The release rate of the drug from the tablets was found to decrease drastically with increase in polymer concentration. Drug release of Entacapone from all the formulations F1 to F5 ranged from 30.21 to 14.21% during the first hour while after 5 hrs, it was between 71.87 and 45.13 %. Increase in the content of polymer decreased drug release. Burst effect was observed at the 1st hour only in formulations containing low polymer concentration F1 to F3. The drug release from formulations F4 and F5 extended up to 12 hrs and 13hrs containing high polymer concentration than F1 to F3. Formulations F1 to F3 showed complete drug release within 7, 9 and 10 hrs respectively as explained in table-5 and figure-2.

Table-5: In vitro Drug Release of Entacapone matrix tablets prepared with HPMC K4M.

Time (Hrs)	Cumulative % Drug Release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	30.21	25.44	21.84	16.44	14.21
2	43.33	35.46	30.42	27.55	20.45
3	50.63	44.2	40.66	34.95	30.1
4	63.44	50.37	47.42	42.91	36.42
5	71.87	60.65	55.12	51.91	45.13
6	86.44	74.04	65.98	58.08	53.86
7	98.32	80.44	72.54	68.1	60.41
8		87.38	83.21	73.24	69.14
9		98.63	90.85	79.67	75.23
10			99.45	88.65	84.34

11				95.76	89.14
12				99.24	95.28
13					99.95

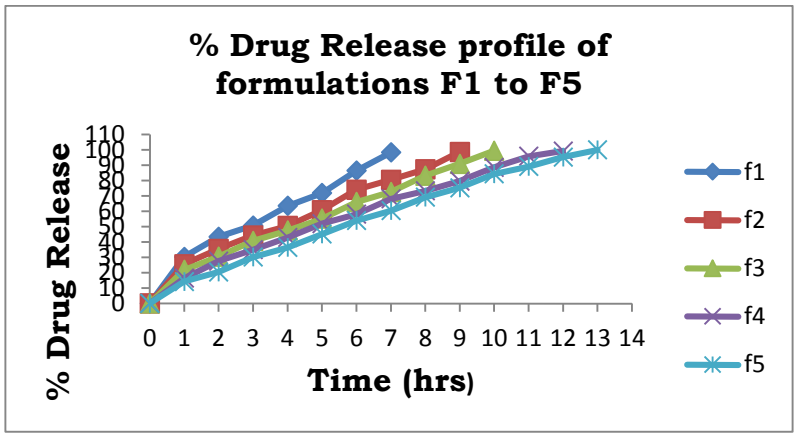

Figure-2: cumulative percentage Drug Release profile of entacapone matrix tablets prepared with HPMC K4M.

***In vitro* Drug Release Kinetics of Entacapone Matrix Tablets Prepared with HPMC K4M:**

The kinetic models used in the assessment of the dissolution data in this study were the Zero order, First order, Higuchi and Hixson-Crowell models while Korsmeyer-Peppas model was used to determine the mechanism of drug release. The dissolution data of the various batches of tablets were fitted into the various kinetic models and their regression values used to assess the best fit. The higher the R^2 value (i.e. the more linear the graph), the better the fit of the dissolution profile to that kinetic model as shown in table-6.

Table-6: *In vitro* Drug release kinetics of Entacapone Matrix tablets prepared with HPMC K4M.

Formulations	R^2values of Kinetic Models					
	Zero order	First order	Higuchi	Hixson Crowell	Korsmeyer peppas	slope (n)
F1	0.995	0.761	0.969	0.634	0.981	0.595

F2	0.995	0.752	0.974	0.577	0.982	0.622
F3	0.998	0.693	0.977	0.390	0.988	0.670
F4	0.995	0.780	0.988	0.414	0.998	0.730
F5	0.996	0.603	0.984	0.350	0.994	0.802

The best fit with higher correlation coefficient was found with zero order model for the formulations F1, F2, F3, F4 and F5 which indicates that the amount of drug release is proportional to the time. The drug release mechanism based upon entrance of the surrounding medium into a polymer matrix where it dissolves and leaches out the soluble drug, leaving a shell of polymer and empty pores. Depletion zone moves to the centre of the tablet as the drug released. Since the boundary between the drug matrix and the drug depleted matrix recedes with time and the thickness of the empty matrix through which drug diffuses also increases with time.

The Krosmeyer peppas graphs of log cumulative percent release against log time was plotted slope “n” was determined. From the above formulation only F4 showed highest regression value of 0.998 and n value is 0.730. Slope values of the formulations F1 to F5 were found to be in the range of 0.595 and 0.802. Therefore it can be inferred that the drug release may have followed anomalous or non-Fickian diffusion.

% Swelling Index of Entacapone matrix tablets prepared with HPMC K4M:

The release of drugs from matrix formulations has been linked to the nature of matrix material, as well as complex processes such as swelling, diffusion and erosion. Table-7 and figure-3 shows the percentage of water absorbed by the matrix tablets produced. It was observed that most of the tablets swelled within the six hours for F1 to F5, showed good swelling behaviour even up to 9 hrs showing the greatest water absorption. Maximum swelling index was observed to be 151.7% in formulation F5 at the end of 9h. All the batches achieved a very good swelling index that correlates to the drug release mechanism. This also proved the assertion that HPMC achieves good swelling in phosphate buffer pH 5.5. It can also be said that the mechanism of release may be due to swelling and subsequent erosion of the matrix to release the active drug.

Table-7: % Swelling Index of Entacapone matrix tablets prepared with HPMC K4M.

Time (Hrs)	Formulations				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	18.53	25.29	54.53	72.24	88.93
3	42.34	53.68	79.21	88.56	102.08
5	52.14	64.52	85.45	99.21	115.97
7	70.95	87.85	105.19	119.58	130.21
9	92.19	101.57	122.22	135.43	151.7

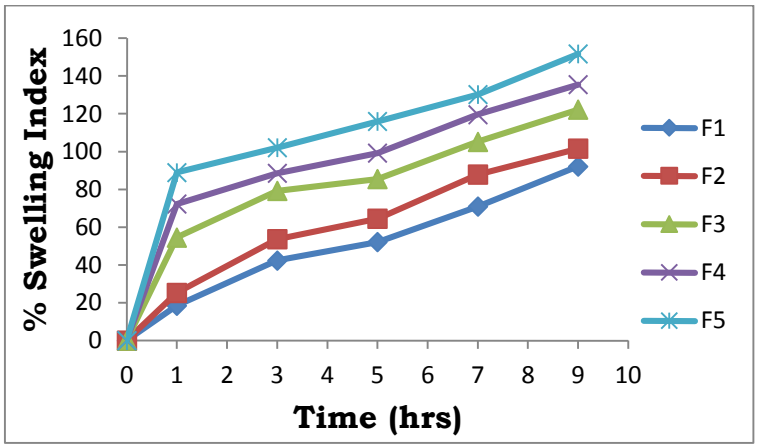

Figure-3: % Swelling Index of entacapone matrix tablets prepared with HPMC K4M.

% Erosion index of entacapone matrix tablets prepared with HPMC K4M:

All the batches achieved a very good erosion index that correlates to the drug release mechanism as shown in table-8 and figure-4. Maximum erosion index was found to be in formulation F1- 61% and minimum in F5- 41% at the end of 9 h. Swelling and erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug-release rate.

Table-8: % Erosion index of entacapone matrix tablets prepared with HPMC K4M.

Time	Formulations				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	16.5	13.7	12	9.5	8
3	27	23	21	18.5	16
5	38	33	31	28	25
7	53	45	40	37.5	35
9	61	55	50	45	41

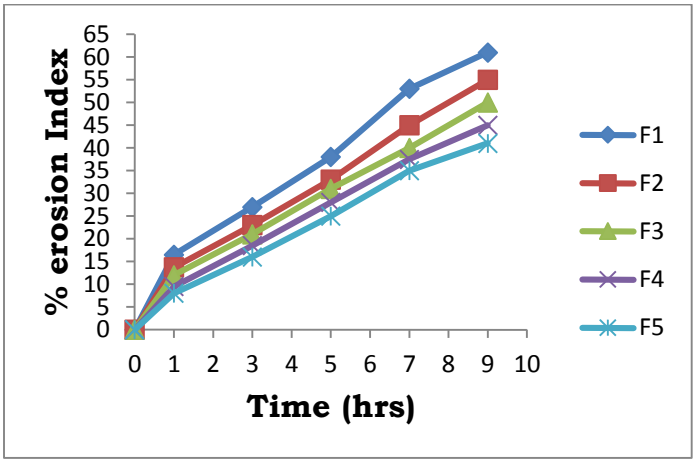

Figure-4: % Erosion index of entacapone matrix tablets prepared with HPMC K4M.

Characterization of Drug and Excipients:

Fourier Transform Infrared Spectroscopy (FT-IR) study:

The physicochemical compatibility of the drugs and polymers was established through FTIR studies. FTIR study was conducted on the selected formulations prepared with combination of polymers such as HPMC K4M. IR spectral analysis of pure Entacapone showed the peaks at wave numbers confirming the purity of drug with standard.

The spectrum peak points of the formulation were similar with that of the pure Entacapone clearly indicating that there is no drug-polymer interaction as shown in figure-5 and 6.

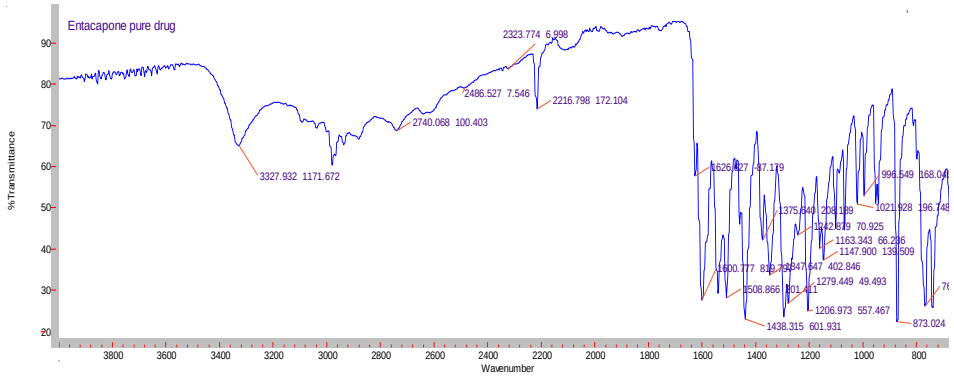

Figure-5: FTIR spectra of Pure Drug Entacapone

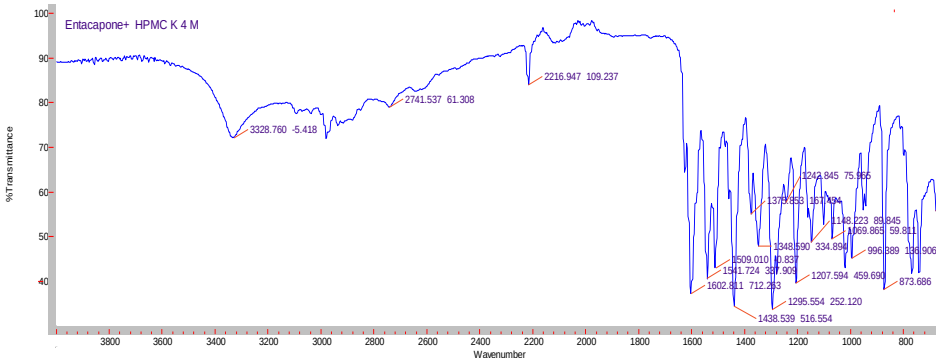

Figure-6: FTIR spectra of entacapone matrix tablets prepared with HPMC K4M

Differential Scanning Calorimetric (DSC) study:

Selected formulations of Entacapone matrix tablets were characterized for DSC. The pure entacapone showed a sharp exothermic peak at 165.9^{0}C. Similar exothermic peaks is observed at similar temperature in the prepared tablets at 163.3^{0}C for HPMC K4M.The above study confirms that there was no drug polymer interaction as explained in figure 7 and 8.

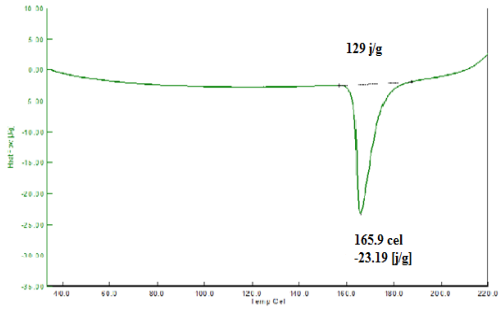

Figure-7: DSC thermogram of Pure Drug Entacapone

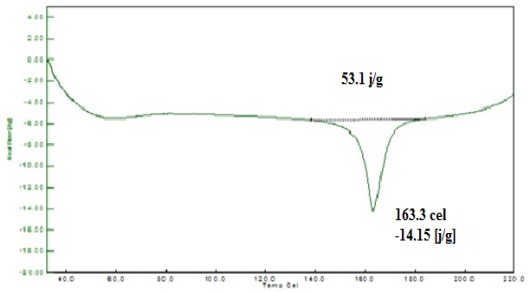

Figure-8: DSC thermogram of Entacapone matrix tablets prepared with HPMC K4M

CONCLUSION:

The present investigation was concerned with the development of entacapone sustained release matrix tablets, using viscosity grades of HPMC K4M by 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 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 upto 18h. This may in turn reduce the dosing frequency, thereby improving patient compliance.

This research study provides useful information for the formulation scientists to formulate and characterize sustained release matrix tablets of entacapone. From the economical point of view, it may be beneficial for the local pharmaceutical firms to adopt such simple technologies for the preparation of sustained release product. The reproducibility and accuracy of formulation was required further in-vivo studies and continuation of stability studies is also recommended.

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