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Formulation and Characterization of Modified Release tablet of Captopril for the Treatment of Hypertension

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ABSTRACT

Modified release formulation has been the first choice for formulators of Pharmaceutical formulation it is due to their versatile potential of releasing the drug in desired rate and release kinetic irrespective of their physiochemical and Biopharmaceutical properties. In this research work an attempt was made to formulate Captopril modified release tablet in order to facilitate its release in desired rate and in optimum concentration , Formulation of Tablet formulation was done by preparing bilayer tablet of the drug in which immediate release layer was optimized by using different concentration of sodium starch glycolate and controlled release tablet was formulated by optimizing the concentration of Hydroxypropyl methyl cellulose K4M then they were united and compressed together to formulate optimized formulation among the prepared formulation batches optimized batch F2 exhibited best results of all the evaluation parameters.

Key words: Captopril modified release tablet, hypertension, *in vitro* drug release.

1. INTRODUCTION

Modified release dosage forms have been developed to deliver drug to the part of body where it will be absorbed, to simplify dosing schedules, and to assure that concentration of drug is maintained over an appropriate time interval. Some formulations like ointments, solutions, or fast dissolving dosage forms are not offered by conventional dosage forms. This thoughtful change is performed by superior formulation design and manufacturing methods dosage forms. Modified release dosage forms are used in research increase the bioavailability of the formulation. The development of modified release dosage form is more useful when selected agent possess different mechanism of action; it also decreases the required doses of drug as compare to the dose available in the marketed conventional drug delivery system. The modified release formulations have been developed to distribute drug to the part of the body where it will be absorbed. The Modified release dosage forms are designed to release drug in a controlled manner to reach safety profile and desired efficacy. [1-7]

1.1 Delayed Release

Onset of drug action starts at later phases (For example, enteric coated tablets are known to show the action when dosage forms reach small intestine.)

1.2 Extended release/Sustained release

The duration of drug action is prolonged for longer time (For example, Sustained release dosage form of any anti-psychotic drug).

1.3 Repeat Action

The dosage form contains two parts: -

First part release by the first order kinetics to reach to the minimum effective concentration (MEC) and Second part is drug release by zero order kinetics to achieve modified release. [8]

Pharmacological therapies either requires or benefit from the administration of drug in a sequential manner. This can be done by a regimen in which the patient follows a prescribed time schedule, but because of patient noncompliance scrupulous adherence to a schedule often requires the assistance of a medical professional. Like chronic diseases such as heart disease, diabetes, asthma are often treated using multi-drug therapies, which are vulnerable to incidences of side effect, poor patient compliance, and slow improvement of patients.

According to world health statistics report, one in three adult's worlds wide has raised blood pressure-a condition that cause around half of all deaths from stroke and heart disease. Hypertension has become a common problem in all over the world due to busy, unbalanced life style and other reasons, so finally this research work has been selected for dissertation work. Drug which was used to develop modified release formulation was Captopril for the treatment of hypertension.

Captopril is selected for the formulation of current research work. This is Antihypertensive agent belonging to the Angiotensin converting enzyme (ACE) inhibitor group. These are used in the treatment of lower BP in hypertension. Captopril main uses are based on its vasodilation and inhibition of some renal function activities. As explain above an attempt was made to formulate the modified release tablet of Captopril and on the basis of characterization of the prepared tablets Optimized formulation was chosen.

2. MATERIALS AND METHODS

2.1 Materials

Captopril was obtained from Wockhard Ltd. Aurangabad. Polyvinylpyrrolidone, HPMC K4M, Microcrystalline Cellulose, Sodium starch glycolate, Talc, Lactose, Sodium dihydrogen phosphate, Potassium dihydrogen phosphate and Isopropyl Alcohol purchased from Central Drug Laboratory, Delhi (CDH).

2.2 Method of Preparation of Modified release tablets

Tablets were prepared by wet granulation technique using single punch manual hand operated machine. Modified release tablets were prepared in two stages. First stage was formulation of sustained release layer. The drug, polymer and Lactose are mixed and compressed produce the first layer. Second stage was formulation of modified release tablets. The drug and Lactose are mixed separately for immediate release layer. The sustained release was placed in punching die. Then contents of immediate release were placed over the sustained release layer tablet and compressed to produce the modified release tablets.

2.2.1 Granulation of the immediate release layer (as loading dose) of Captopril

Captopril, Lactose, Microcrystalline cellulose were mixed with Sodium starch glycolate for 15 minutes in pestle mortar and passed through 40# sieve. Blend was prepared with a solution of polyvinylpyrrolidone in isopropyl alcohol. The wet mass was granulated and granules were dried at 40^0C for 1 hour in an hot air oven and shifted. Then granules were mixed with talc for 5 minutes in a pestle-mortar and then processed for compression by using single-punch tablet machine. The final weight of IR layer was fixed to 200mg. Composition of IR layer is presented in Table 1.

2.2.2 Granulation of the sustained release layer (as maintenance dose) of Captopril

The detailed composition of formulation for the SR layer is presented in table 9. HPMC K4M and lactose were blended with Captopril, PVP K30 for 15 minutes in pestle mortar and the mass was prepared using isopropyl alcohol as a granulating fluid. Then passed the mass through sieve 40# and granules were allowed to dry in oven at 40^0C for 30 minutes. The dried granules were sifted and mixed with talc for 5 minutes in polybags. Finally, all the granules were weighed to adjust the final weight of the individual tablet taking into consideration its loss during operational handling. The final weight of formulation was kept at 200mg.

2.3 Characterization of Granules

2.3.1 Angle of repose

It is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. Angle repose of granules was determined by the funnel method. A glass funnel was held in place with clamp on a ring support over a glass plate. Granules were transferred in to funnel keeping the orifice of the funnel blocked by the thumb. The thumb was removed and when the granules were emptied from the funnel, the diameter and the height of the granules cone was measured and the angle of repose was calculated by using following equation.

$$\text{Tan } \Theta = h/r$$

Where h is the height of the pile and r is radius of the Pile

2.3.2 Bulk density

The powder blend of modified release tablet was allowed to pass through sieve no. 20 to break of clumps, if any accurately weighed of powder was placed in measuring cylinder of 50 ml and

initial level of volume V_0 was noted. The bulk density was calculated in g/cm^3 by the formula

Bulk density = Mass of powder taken (m) / Bulk volume (V_0)

2.3.3 Tapped density

Tapped density determined by taking small quantity of granules sample carefully introduced into 50ml measuring cylinder. Cylinder was dropped at 2 sec. intervals on hard wood surface 100 times from height 1 inch. Tapped density of each sample was obtained by dividing weight of sample in gm. By final tapped volume of sample contain in cylinder.

Tapped density =Mass of powder taken (M) / Tapped volume (Vf)

2.3.4 Compressibility index

It was determine by taking small quantity of granules sample in 10 ml measuring cylinder. The height of the sample was measured before and after tapping.

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

2.3.5 Hausner's ratio

It is the number that is correlated to the flow ability of a powder/granules material. It is calculated by the formula:

Hausner's ratio = Tapped Density / Bulk Density

2.3.6 Compression of Modified release tablets

Granules of both the layer obtained were compressed into 400mg modified release tablet. 0.2 gm of sustained dose granules and 0.2gm of immediate dose granules were weighed and one by one both layers were filled and compressed into modified release tablets by using a single punch tablet machine. A flat-faced punch was used for preparing tablets.

2.4 Evaluation of Bilayer Tablets

2.4.1 Weight variation

20 tablets were selected at random from each batch and the average weight was calculated. The batch passes the test for weight variation if not more than two of the individual tablet weight deviates from the average weight by more than the percentage and none deviate by more than twice the percentage.

2.4.2 Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on the hardness of tablet. The hardness of each tablet is measured by Monsanto hardness tester. Its unit is Kg/cm^2.

2.4.3 Friability

Friability is evaluated by the use of Roche friabilator. 20 tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks. The tablet fall 6 inches in each turn for four minutes at the rate of 25 rpm (revolution per min.). After that the tablets are weighed and the final weight is noted down. The final weight determine the loss due to abrasion which measures the tablet friability. A weight loss of not more than 1% of the weight of the tablets during the friability test is considered generally acceptable. The loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = 1-Loss in weight / Initial Weight × 100

2.4.4 Disintegration test for IR layer

The disintegration test of the tablets was carried out using USP disintegration test apparatus. Six tablets were placed individually in each tube of the apparatus, test was performed in 0.1 N HCl with the discs. The temperature of the water bath was maintained at 37 ± 0.5^0through out during the test and disintegration time was measured. The tablet passes the test if all six have disintegrated is not more than 5 minutes. If one or two tablets fail to disintegrate, then the test is

2.4.5 In vitro drug release studies

Drug release of the modified release tablet was carried out using USP type II (Paddle) apparatus at 100rpm. 900ml of phosphate buffer (pH 7.4) was used as a dissolution media maintained at 37 ± 0.5^0C. 5 ml of the sample was withdrawn at preselected regular intervals up to 12 hours and the same volume of the fresh dissolution medium was replaced to maintained the volume constant. The samples withdrawn were filtered through a whatman filter paper and the drug content in each sample was analyzed after suitable dilution with a UV/Visible spectrophotometer at 212nm for Captopril respectively and cumulative percentage release of drug was calculated and determined.

2.4.6 Drug release kinetics

The drug release kinetics was studied by various kinetics models such as zero order, first order, Higuchi model and Koresmeyerpeppas release kinetics.

3. RESULT AND DISCUSSION

3.1 Spectrophotometry of Captopril

The standard curve of Captopril in 0.1 N HCl was prepared. The calibration curve was plotted which gives good linearity. The value of r^2 was found to be 0.991 in 0.1 N HCl, which indicate drug follows Beer-Lambert's law within the specified concentration range.

3.2 Characterization of Granules

The angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio of sustained and immediate release granules are shown in table 3,4 and 5.

From the observation tables, it was found that angle of repose of immediate and sustained release granules were more than 25° an angle of repose more than 25 °indicates good flow. This property was further supported by Carr's index value which was also found above 18 % and powder having the Carr's index value less than 25% shows good flow property. Even Hausner's value was also found more than 1.34. Hence on the basis of above results we can say sustained and immediate release granules have good flow properties.

3.3 Evaluation of Modified release tablets

The final prepared tablets were evaluated for their various physico-chemical properties. The Weight variation, Thickness, Friability and Hardness of modified release tablet are shown in table.

3.4 *In vitro* Drug Release Studies

In vitro drug release test were to assure that the modified release tablet of Captopril are deliver to the target area, and to elucidate the release kinetic for the developed formulation. The drug release of Captopril loaded modified release tablets of optimized formulation of F-2 was performed in PBS 7.4 pH. The dug release pattern from modified release tablet of Captopril was in sustained manner, in contrast to dissolution of pure drug. The drug release studies of F2 has been carried out. The cumulative drug release (%CDR) was found to 70.31%. However, the release of Captopril from the modified release tablet made with HPMC K4M formulation F-2 shows the best release pattern. Release data has been shown in Fig No 1.

3.5 *In vitro* Drug Release Kinetics

The data obtained for in-vitro release where fitted into equations for the zero order, first order, Higuchi and Peppas release model. The interpretation of data was based on the value of the resulting regression coefficient.

The zero order rate describe the system where the drug release rate is independent of its concentration graph-2, shows the cumulative amount of drug release V/S time for zero order kinetic. The first order rate describe the release from system where the release rate is concentration dependent, which is shown in graph - 3. The Higuchi model explain the release of drug from and insoluble matrix as a square root of time dependent process based on fickian diffusion graph-4 illustrate Higuchi release model.

The calculated regression coefficient for zero order, first order, Higuchi and peppas was shown in table. It was found that *in-vitro* drug release of Captopril modified release tablet was best explained by Zero order as the plot showed the highest linearity. Therefore, the release seems to fit the zero order.

From the value r^2 obtained as shown below in the table it was found that the maximum r^2 value is shown in zero order release kinetics. Thus, the optimized formulation followed the zero-order release kinetics.

3.6 Differential Scanning Calorimetry (DSC)

The DSC of pure drug Captopril, polymer HPMC K4M, immediate release formulation, sustained release formulation and final formulation was formed. Incompatibility between drugs and excipients can alter stability and bioavailability of drugs, thereby affecting its safety or efficacy. Study of drug-excipients compatibility is an important process in the development of stable solid dosage forms, despite the importance of drug – excipients compatibility testing, there is no universally accepted protocol for this purpose. The term thermal analysis refers to a group of techniques in which physical property of a substance or reaction products is measured as a function of temperature whilst the substances is subjected to a controlled temperature program. DSC technique involves the application of a heating or a cooling signal to a simple and a reference.

DSC was used for thermal analysis of drugs , mixture drugs and excipients. Individual sample of Captopril (2.588mg) was weighed and scanned in the temperature range of 30^0 to 330^0 at the heating rate of 10^0C/min under an atmospheric condition of dry nitrogen. Thermogram obtained of all sample.

A formulated modified release tablet was also subjected to this procedure for drug-excipients compatibility study. 3.195mg of sample powder of modified release tablet was weighed and processed for the above method for the DSC. In thermogram Fig 1 The sharp endotherm indicates melting point of the drug Captopril between 100 to 103° and this endotherm was observed in the

immediate release layer thermogram Figure 4 and sustained release layer thermogram figure 5.

4. CONCLUSION

Modified release dosage forms are drug delivery systems which, by virtue of formulation and product design, provide drug release in a modified form distinct from that of the conventional dosage forms. Drug release can either be sustained or immediate in nature. So modified release dosage forms and it has several applications in pharmacy like reduction in drug blood level fluctuations, reduction in frequency of dosing, enhanced patient compliance reduction in incidence of adverse side effects, reduction overall healthcare costs also.

Drug absorption in the GIT is a highly variables process, prolonging gastric retention of the dosage forms and extended the time of drug absorption.

Modified release tablets are prepared with various polymer successfully by the wet granulation technique. The amount of drug released from tablet could be enhanced.

In vitro data obtained from modified release tablets of Captopril showed optimum weight variation, hardness, thickness, friability disintegration time and prolonged drug release. Thus, the prepared modified released tablets may prove to be potential candidate for the treatment of hypertension as a modified release drug delivery system. The formulations were evaluated for various micromeritics and characteristics studies. It increase the bioavailability of dosage form with prolong effect. Hence improve the patients compliance.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

Table 1. Composition of the Immediate release layer (as drug loading layer)

S. No.	Ingredients	F_1	F_2	F_3	F_4	F_5
1	Captopril	6	6	6	6	6
2	Lactose	30	50	70	90	110
3	MCC	55	45	35	25	15
4	SSG	79	69	59	49	39
5	PVP K30	20	20	20	20	20
6	Talc	10	10	10	10	10
7	IPA	q. s	q. s	q. s	q. s	q. s
8	Total weight (mg)	200	200	200	200	200

Table 2. Different formulation batches for different concentration excipients

S.No.	Ingredients	F_1	F_2	F_3	F_4	F_5
1	Captopril	30	30	30	30	30
2	HPMC K4M	25	45	65	85	105
3	Lactose	115	95	75	55	35
4	PVP K30	20	20	20	20	20
5	Talc	10	10	10	10	10
6	IPA	q. s	q. s	q. s	q. s	q. s
7.	Total weight (mg)	200	200	200	200	200

Table 3. Angle of repose of sustained release layer

Formulation Code	Angle of repose
F1	29.7^0
F2	30.07^0
F3	24.7^0
F4	27.9^0
F5	30.1^0

Table 4. Bulk density and Tapped density batches of sustained release layer

Formulation Code	Bulk density (g/cm^3)	Tapped density (g/cm^3)
F1	0.33	0.59
F2	0.28	0.38
F3	0.37	0.52
F4	0.30	0.40
F5	0.28	0.38

Table 5. Percentage Compressibility Index, Hausner's ratio of sustained release layer

Formulation Code	% Compressibility Index	Hausner's Ratio
F1	44.06	0.62
F2	25.19	1.33
F3	28.84	0.52
F4	25.0	0.45
F5	26.31	0.49

Table 6. Hardness of different batches of modified release tablet

Formulation Code	Hardness (Kg/cm^2)	Friability (%)	Weight Variation
F1	9.5	0.43	PASS
F2	10.0	0.42	PASS
F3	8.5	0.46	PASS
F4	9.0	O.55	PASS
F5	9.5	0.41	PASS

Table 7: Regression value of formulation F-2 for different release kinetics models

S. No	r^2	Kinetic model
1	0.996	Zero order
2	0.973	First order
3	0.966	Higuchi model
4	0.975	Peppas model

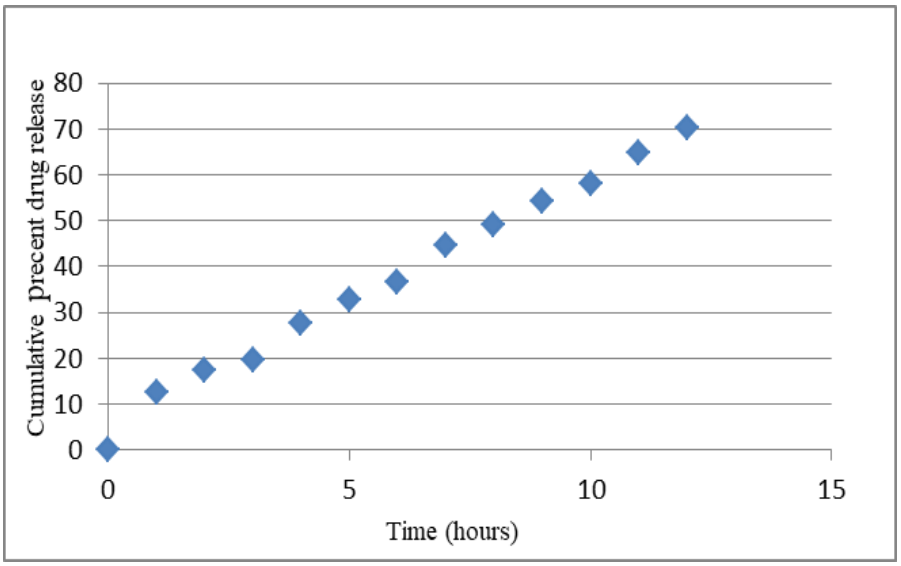

Fig.1: Cumulative percentage release of the optimized formulation F2

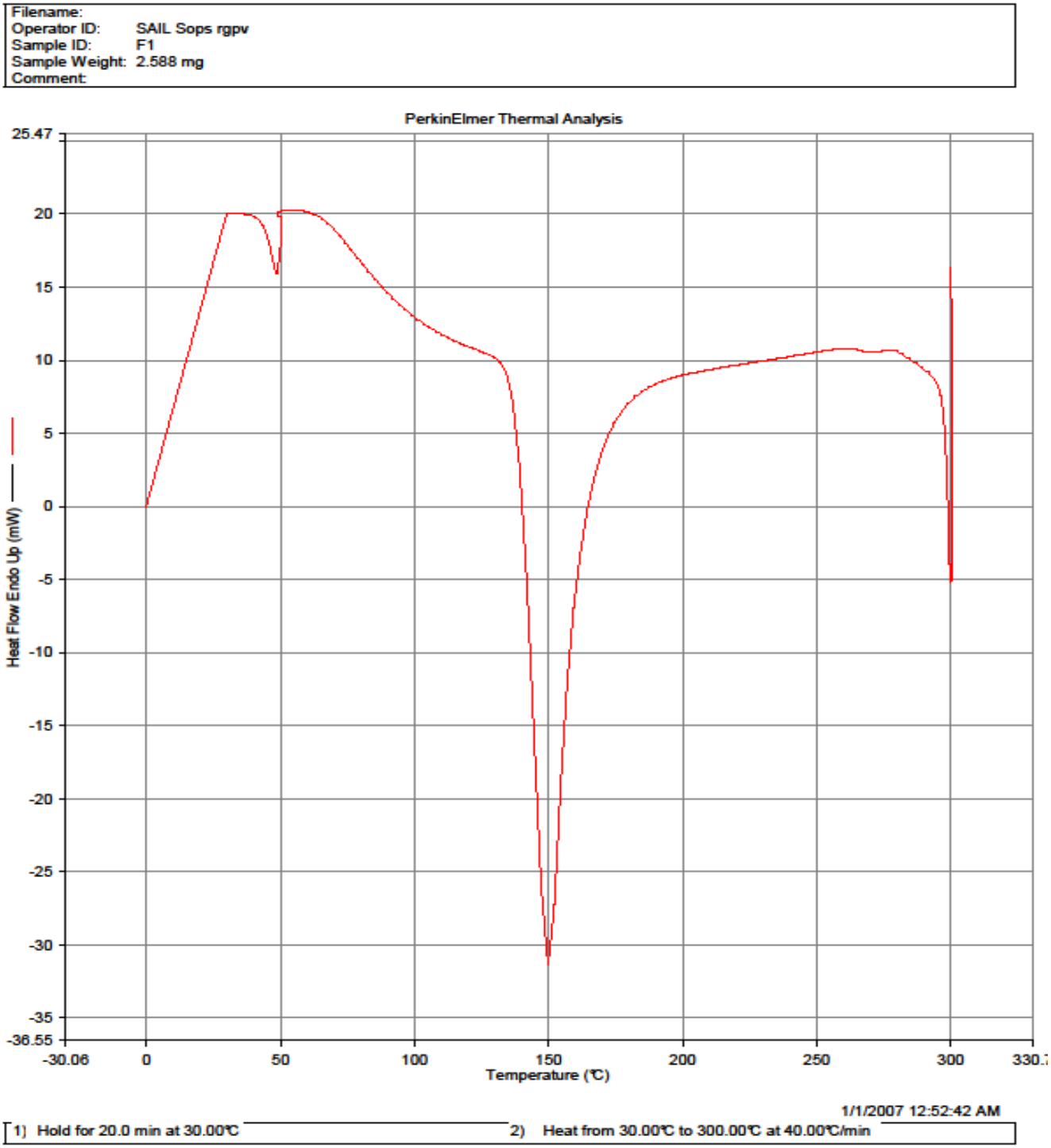

Fig.2: The DSC of HPMC

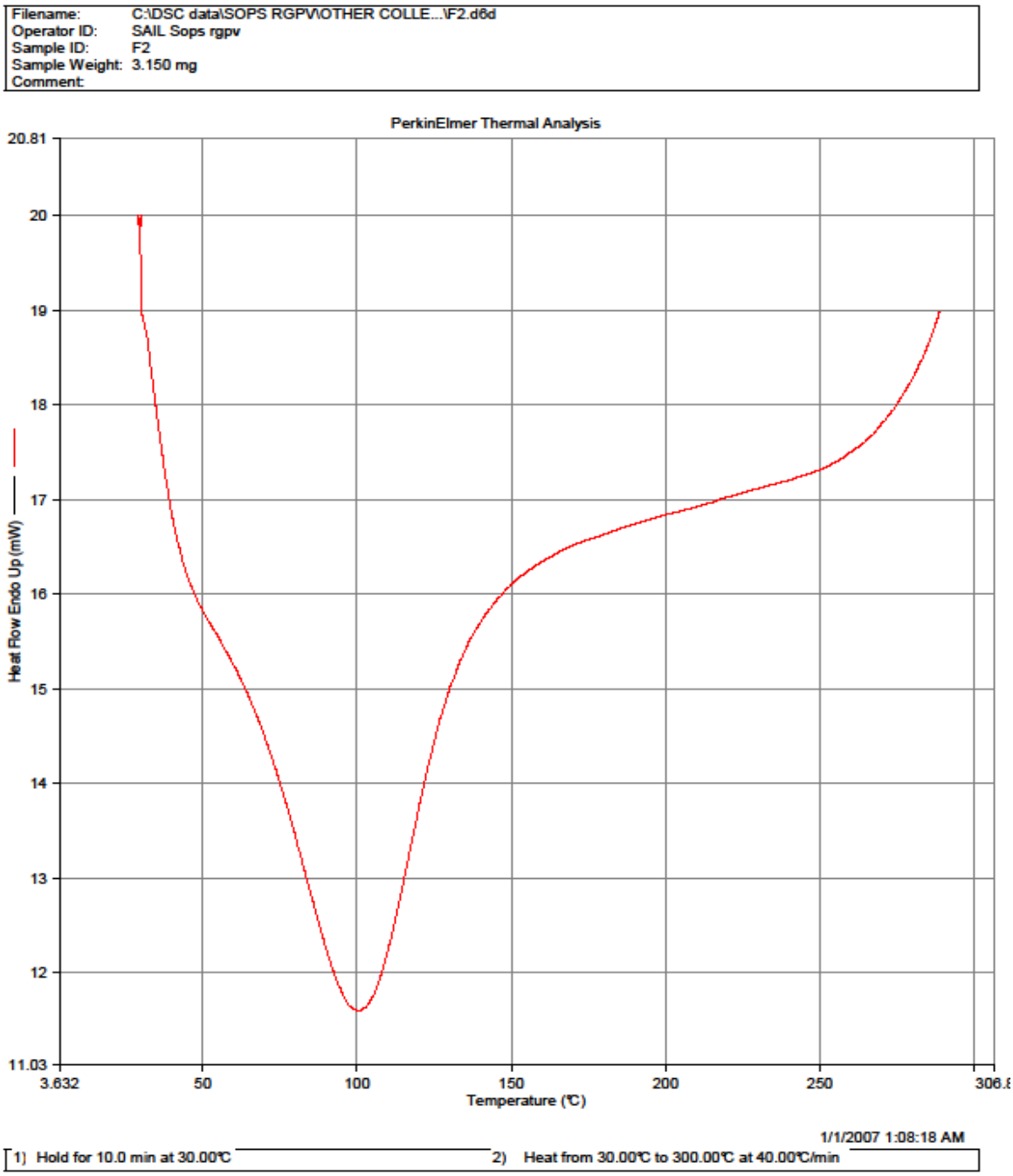

Fig.3: DSC of Captopril

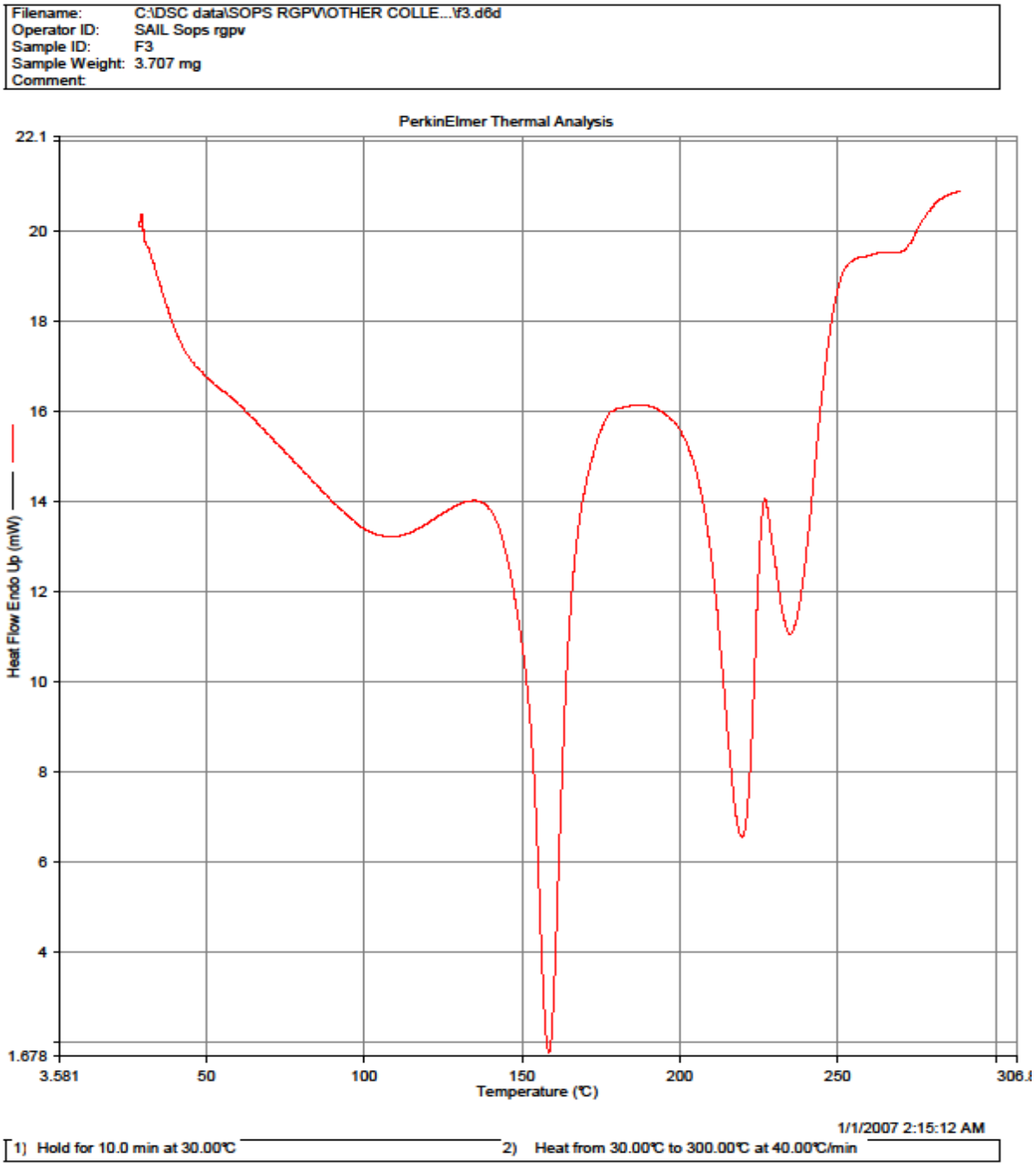

Fig. 4: The DSC of Immediate release formulation

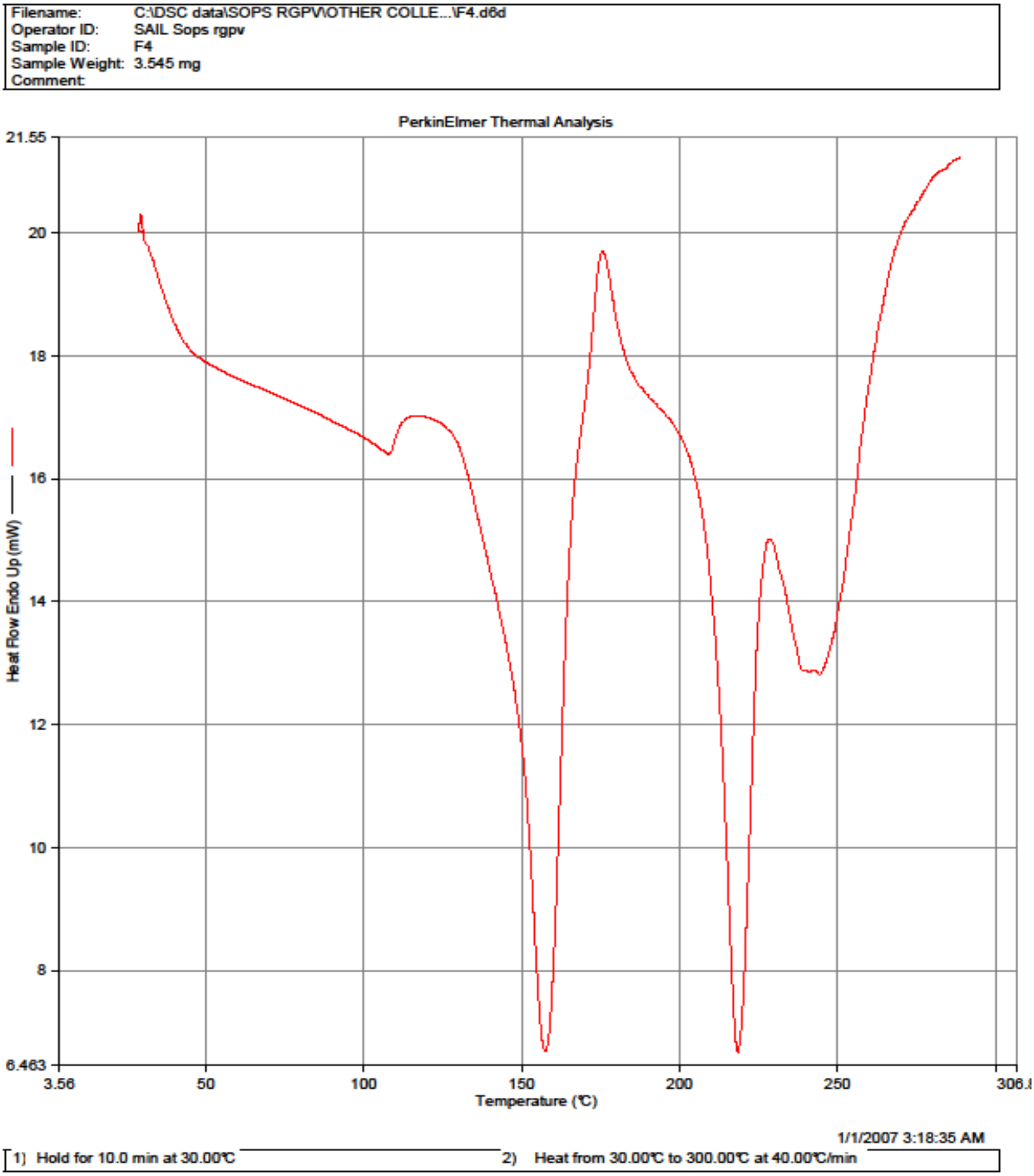

Fig.5: The DSC of Sustained release formulation

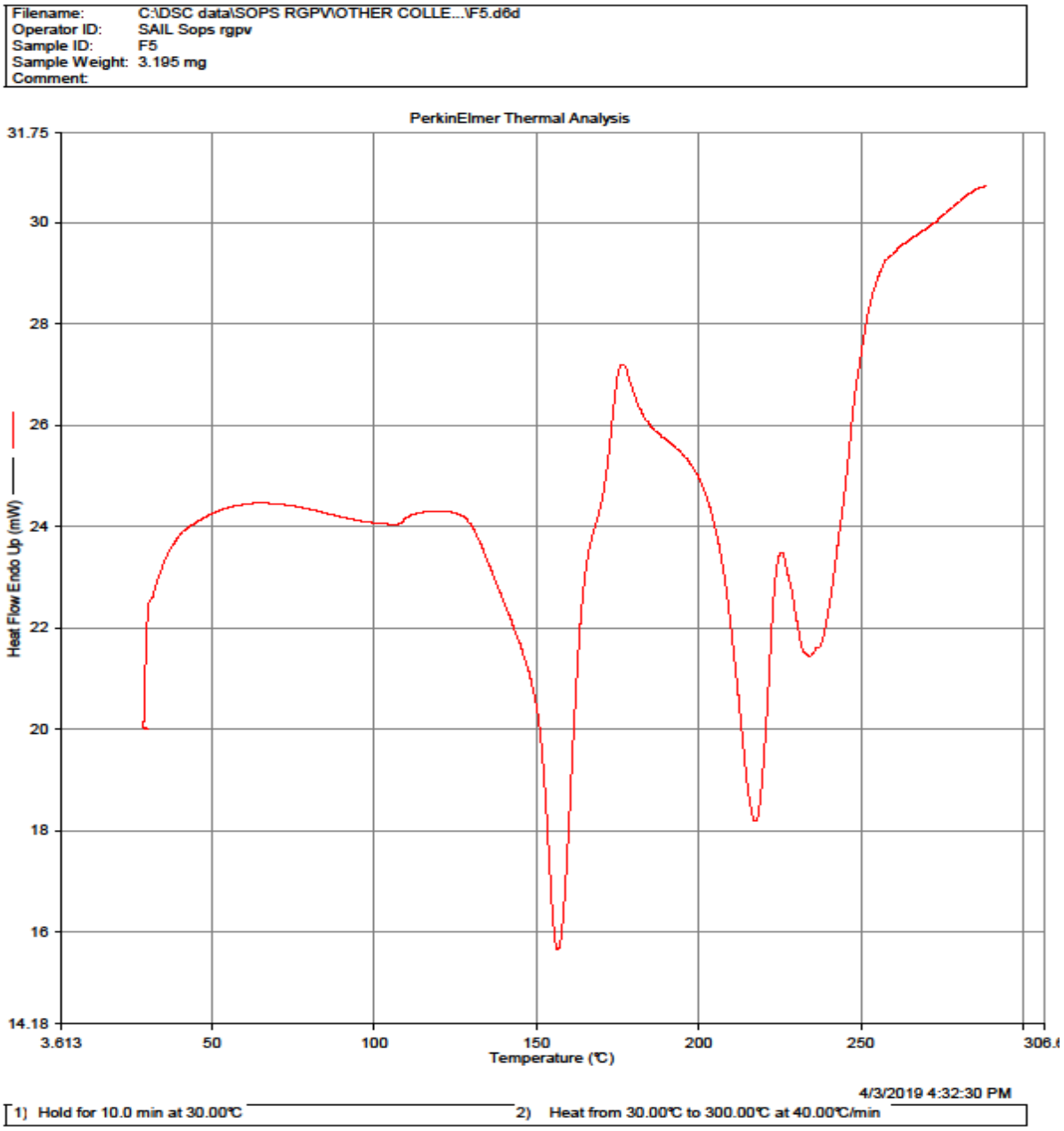

Fig. 6: The DSC of Modified release tablet of Captopril

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