Research Article

Formulation and Evaluation of Biphasic Drug Delivery System of Montelukast Sodium for Chronotherapy

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ABSTRACT

In the present study, we have designed Montelukast sodium granules and tablets filled in HPMC capsule system, which is presented as a biphasic delivery system. Montelukast sodium is used in the treatment of chronic asthma, and to relieve symptoms of seasonal allergies. Montelukast sodium biological half-life is 2.5 to 5.5 hrs, thereby decreasing bioavailability up to 64%. So in order to improve the bioavailability and efficacy we have designed granules and mini-tablets filled in HPMC capsule system, which is presented as a biphasic delivery system. The outer layer that fills the void spaces between the mini-tablets was formulated to release the drug in a very short time (fast release), while the mini-tablets provided a sustain release. Fast releasing component comprises superdisintegrant crospovidone, while mini-tablet was formulated using different concentration of HPMC and Ethyl cellulose to obtain different drug release rates. The *In-vitro* performance of these systems showed the desired biphasic behavior. The drug contained in the fast releasing phase (Granular powder) dissolved within the first 10 min, whereas the drug contained in the mini-tablets was released at different rates, depending upon composition of mini tablets. The *in-vitro* performance of the best formulation showed the desired behavior, the drug contained in the granules for immediate release dissolved within the first 10 min, whereas the drug contained in the sustained release tablets was released over a period of 12 hrs. The formulation GMTFCS-4 shows 29.55 % of montelukast sodium release was released in 1hrs as an immediate-release phase and 99.92% of montelukast sodium was sustained for a period of 12 hrs. From this, study it can be concluded that, granules and mini-tablets filled in HPMC capsule systems containing Montelukast sodium shows both sustained release as well as immediate release may improve the bioavailability and efficacy.

Keywords: Biphasic systems, montelukast sodium, sustained release mini-tablets.

INTRODUCTION

Biphasic delivery systems are designed to release a drug at two different rates or in two different periods of time: they are either quick/slow or slow/quick. A quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time and in slow/quick release system provides release vice versa[1].

Biphasic release system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include non-steroidal anti-inflammatory drugs (NSAIDs) antihypertensive, antihistaminic, and anti-allergic agents[2]. Generally, conventional controlled dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. While immediate release granules give fast release to provide rapid onset of action, but fails to provide longer duration of action. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract[3]. On the basis of these considerations, we have proposed a new oral delivery device, in the form of a double-component tablet and granules, in

which the one portion is formulated to obtain a prompt release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second portion is a sustain release matrix, which is designed to maintain an effective plasma level for a prolonged period of time[4]. This concept can be used to produce a biphasic delivery system combining a fast release together with the slow release period of the drug, provided that the excipients powder that fills The void spaces between the mini-tablets incorporate a part of the total drug dose. This system can produce a rapid rise in the plasmatic concentrations for some drugs (such as analgesic, anti-inflammatory, anti hypertensive and antihistaminic agents) that are requested to promptly exercise the therapeutic effect, followed by an extended release phase in order to avoid repeated administrations[5]. The montelukast sodium is a leukotrine receptor antagonist (LTRA) used for the maintenance treatment of asthma, chronic asthma attacks and to relive symptoms of seasonal allergies[6]. The main drawback of conventional montelukast formulation is that it undergoes hepatic first pass metabolism. Thus, it shows plasma or biological half-life 2.5 to 5.5 hrs[7], there by decreasing bioavailability upto 64%[8].

Compressed mini-tablets systems are presented as a biphasic delivery system. The outer layer that fills the void spaces between the mini-tablets was formulated to release the drug in a very short time (fast release), while the mini-tablets provided a sustained release. Fast releasing component comprises superdisintegrant crospovidone, while mini-tablet was formulated using different concentration of HPMC and Ethyl cellulose. The *In-vitro* performance of these systems showed the desired biphasic behavior[9]. Prepared immediate release granules and sustained release mini tablets are filled in the HPMC capsule. The advantage of the HPMC capsule is the HPMC capsules exhibited lower moisture contents compared to gelatin capsules (*e.g.* 6% and 14% respectively at 50% RH) that have shown to be more hygroscopic. The main advantage of HPMC capsules over gelatin capsules could be because of their vegetable source which has wider customer acceptance. Hindu or Buddhist for example rely on vegetable sources for their nutrition[10-14]. The drug contained in the fast releasing phase (Granular powder) dissolved within the first 5 min, whereas the drug contained in the mini-tablets was released at different rates, depending upon composition of mini-tablets [15, 16]. In the present study, we have designed granules and mini-tablets-in-capsule systems. The system comprises of immediate release granules and sustained release mini-tablets filled in HPMC capsule.

MATERIALS AND METHODS

Montelukast Sodium was obtained as a gift sample by Zydus health care (east Sikkim), and Morepen Pharma Pvt. Ltd, Solan (Delhi), Crospovidone was purchased from Rajesh chemicals, Mumbai, HPMC (15 cps), D-Mannitol and Sodium lauryl sulphate were purchased from SD Fine Chem Lab, Mumbai, Ethyl cellulose (18-22cps) and PEG-6000 were purchased from Loba Chemie Pvt. Ltd, Mumbai, Anhydrous dibasic calcium phosphate, and magnesium stearate were purchased from Himedia Chem Lab, Mumbai, and Aerozil was purchased from Sisco Research laboratories Pvt. Ltd. Mumbai. HPMC capsules were obtained as a gift samples from ACG Associated capsules Pvt Ltd, Mumbai.

Preparation of the biphasic delivery system[17]

The qualitative and quantitative composition of the different formulations of the sustain release tablet can be seen in **Table 1 and 2.**

Dose calculation of immediate-release[18]

The pharmacokinetic parameters of drug were utilized for the calculation of theoretical drug release profile for coated mini-tablet-in-capsule system. The immediate-release part of montelukast sodium was calculated using the following equation.

$$D_L = C_{max} V_d$$

Where C_{max} is maximum plasma concentration, and V_d is volume of distribution.

Immediate release component (Granules): Microcrystalline cellulose (Avicel PH 102) was used because of its good compaction and disintegration properties. Crospovidone was used as a super disintegrant to obtain an immediate release of the drug. The granules were prepared by wet granulation method. The composition of immediate release granules were mentioned in **Table 1**.

Sustained-release component (SRMT): The SRMT contained various EC to HPMC ratio (60:40, 70:30, 75:25 80:20, 85:15) as controlling agents. The ingredients consisting of Montelukast Sodium, lactose, HPMC (5 cps), ethyl cellulose were passed through 60 mesh (250 µm) separately and dry mixed. The dry mixing was carried at a slow speed for 10 min and the blend was granulated with 10% w/v alcoholic solution of PVP K-30 for 5 min. The resulting wet mass was immediately passed through a 16 mesh screen (1000 µm). The granules obtained were dried for 1 hrs in a thermostatic hot air oven maintained at 30-35° C to a moisture content of 2 to 3 %. The dried granules were passed through the same sieve (1000 µm) to break the lumps and blended with magnesium stearate and talc. The lubricated granules were compressed into tablets weighing 120mg using 6.3 mm round convex punches in a rotary tablet press (Rimek mini press, model RSB-4, M/S: Karnavati engineering, Ahmedabad) to a hardness of 3 kg/cm^2.

Granules and Mini-tablets filled HPMC capsule system (GMTFCS): The tablets filled HPMC capsule system comprises of immediate-release granules and 3 sustained-release tablets. The compositions of various GMTFCS were mentioned in **Table 3**.

Evaluation of SRMT granules[19, 20]: The powder blend was subjected for pre-compressional parameters like angle of repose**,** bulk density and tapped density, compressibility index and Hausner's ratio.

Evaluation of mini-tablets[19, 20]:

Hardness test: The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm^2. Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability: A friability test was conducted on the mini-tablets using an veego friabilator. Twenty mini-tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The mini-tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The drum was rotated at 25 rpm for 4 min after which the mini-tablets were removed. Any loose dust was removed from the mini-tablets as before and the tablets were weighed again (W_{final}).The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

% Friability of mini-tablets less than 1% is considered acceptable.

Weight variation: The weight variation test was conducted by weighing 20 randomly selected mini-tablets individually, calculating the average weight and comparing the individual mini-tablet weights to the average. The specification of weight variation is 10%.

Uniformity of thickness: The tablet thickness was measured using screw gauge.

***In-vitro* disintegration time[21]:** The *in-vitro* disintegration of the core mini-tablets of SRMT was determined using disintegration test apparatus as per I.P specifications. Place one tablet in each of the six tubes of the basket. Add the disc to each tube and run the apparatus using 900ml of 0.5% SLS in distilled water as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in distilled water maintained at 37 ^{o}C.

Drug content uniformity[22, 23]: Five mini-tablets weighted and crushed in a mortar then weighed powder contained equivalent to 10 mg of drug transferred in 100ml of 0.5% of SLS solution to give a concentration of 100µg/ml. Take 15ml of this solution and diluted it upto 100 ml with 0.5% of SLS solution to give a concentration of 15µg/ml. Absorbance measured at 342 nm using UV- visible spectrophotometer.

***In-vitro* release testing[21]:** Dissolution rate of montelukast sodium from all formulations were performed using Electro lab dissolution apparatus (USPXXIII) with paddle. The dissolution fluid was 900ml water with 0.5% w/v SLS at a speed of 50 rpm and a temperature of 37^{o} C were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filler of 0.5µm at different time intervals, suitably diluted and assayed for montelukast sodium by measuring absorbance at 342 nm. The dissolution experiments were conducted in triplicate. For all tests 5ml samples of the test medium were collected at set intervals (1, 2, 4, 6, 8, 10, 12 hrs) and were replaced with equal volume of 0.5 % SLS in distilled water.

RESULTS AND DISCUSSION

Evaluation of sustained granules

The prepared granules of all the formulations were subjected for various pre-compressional evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio. Results of all the pre-compressional parameters performed on granules of SRMT shown in **Table 4**. The results of angle of repose (<30) indicates good flow properties of the granules. This was further supported by lower compressibility index values. Generally compressibility values up to 15% results in good to excellent flow properties.

Evaluation of sustained release mini-tablets: The data obtained from post-compression parameters for the core tablets of SRMT such as thickness, diameter, hardness, friability, average weight, and drug content is shown in **Table 5**. For the core tablets of SRMT, hardness test indicated good mechanical strength and was found between the range of 2.85 - 3.14 kg/cm^2. Friability is less than 1% indicated that tablets had a good mechanical resistance. Thickness of the core tablets for SRMT was found to be in the range of 2.86 - 3.02 mm. All the formulations passed the weight variation test i.e., average percentage weight variation was found to be within the pharmacopoeial limits of ±10% and the average weight of the core tablets was found to be 120 mg for SRMT. The drug content of SRMT was found to be 97.96 - 99.98 %.

The results of *in-vitro* drug release studies of SRMT were given in **Table 6** and graphical representation was shown in **Fig 1**. These results demonstrate that the dissolution rate and extent of drug release decreased with increasing ethyl cellulose content in the tablets. Hence, the most suitable sustained-release mini-tablet seems to be SRMT-5 releasing 99.02% of montelukast sodium within 12 hrs. The SRMT-1 shows lowest drug release around 98.49 % of montelukast sodium within 6 hrs.

A biphasic oral delivery system was developed by compressing granules and mini-tablets into a HPMC capsules. The compressed mini-tablets showed slight deformation and no fragmentation. Because of their physical characteristics, mini-tablets tend to keep their integrity after compression, making more difficult the fracturing process of these subunits. This technology may be achieved by fast/slow delivery system. This is characterized by an initial rapid release phase, corresponding to the drug release contained in the powder layer filled between mini-tablets, followed by a period of slow release, corresponding to the drug release of mini-tablets. The proposed fast/slow delivery devices show a wide flexibility in the modulation of the delivery program.

In order to develop an optimized sustained release dosage forms, we tested GMTFCS comprising different release profile of granules and tablets (SRMT) in a

HPMC capsule (size 0). The results revealed that formulation GMTFCS-4 was releasing 29.55% of montelukast sodium within an hour as an immediate release phase and the sustained release phase was prolonged for a period of 12 hrs around 99.92 % drug released, and it was found to be the most suitable combination to have an immediate as well as sustained release of drug. The drug release results of GMTFCS were given in **Table 7** and graphical representation was shown in **Fig 2**. Hence, GMTFCS-4 was considered as the best formulation releasing montelukast sodium both as an immediate and sustained-release phase.

Drug excipients interaction studies: The characteristic absorption peaks of pure drug montelukast sodium and promised mini-tablet formulations were shown in **Fig 3**. Drug taken for the present study of formulation is montelukast sodium. It has got tertiary hydroxyl groups which have exhibited a broad peak around 3300 cm^{-1} and a carboxylic acid peak which is in the form of a salt has exhibited a strong peak near 1700 cm^{-1}. Numbers of aromatic C-H peaks are also observed between 2900 cm^{-1} to 3000 cm^{-1}.

The IR Granules contains montelukast sodium, and HPMC. The HPMC contains number of hydroxyl groups in a molecule which is indicated by broad hump at 3500 cm^{-1}. Similarly, to above instead of aromatic C-H number of aliphatic C-H are observed near 2900 cm^{-1}. In SRMT-3 and SRMT-4 absorption peak is absorbed at 3400 cm^{-1} and another peak at 1700 cm^{-1} corresponding to the carboxylate and carbonyl residues. All the peaks corresponding to three constituents were found to be present in its higher spectra indicating that none of the functional groups of either drug or polymers have undergone any chemical reaction.

DSC studies: The thermograms of pure drug and mini-tablet formulations were shown in **Fig 5.** The drug montelukast sodium subjected for DSC studies give very sharp peak at 139.8^{o} C with in the range of 1.0^{o} C indicating the sample is in the pure form and exhibited a sharp melting range.

When the drug is taken in IR Granules were subjected for DSC measurements which have showed a wide range of melting process which has started at 165.39^{o} C and completed at 172.90^{o} C with a range of 7^{o} C. In the next SRMT-4 and SRMT-5 batches, in these cases, during the DSC measurement the formulation has started the melting process at 164.37^{o} C and completed at 175.12^{o} C. This more than 10^{o} C and 8^{o} C. In all the 3 cases suggesting that formulation is a mixture of drug and excipients but not the reaction product. Hence, drug in all these cases is present in the free form for any biochemical process.

CONCLUSION

A novel biphasic granules and mini-tablets filled in HPMC capsule system was developed by filling granules and mini-tablets into an empty HPMC capsule shell which releases 29.55 to 37.40 of the total dose within 60 min. Formulations GMTFCS-1 to GMTFCS-4 shows 95 % of drug releases within 8 hrs, 9 hrs, 10 hrs, and 12 hrs respectively. Among all the formulations GMTFCS-4 can be stated as the best formulation as it releases the initial dose i.e.; 29.55 % within first hours and then sustain the release up to 12 hrs, which would permit a treatment regimen of two doses per day.

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Table 1: Composition of Montelukast sodium immediate release granules

Ingredients	Quantity (mg)
Montelukast sodium	3.6
Crospovidone (CP)	12
Microcrystalline cellulose	50
Mannitol	32.4
HPMC (5 cps)	20
Mg. stearate	2
Total Weight	**120**

Table 2: Composition of Montelukast sodium sustain release mini-tablet

FC	SRMT-1	SRMT-2	SRMT-3	SRMT-4	SRMT-5
MS	2.14	2.14	2.14	2.14	2.14
HPMC(5 cps)	40	30	25	20	15
Ethyl Cellulose	60	70	75	80	85
Lactose	15.86	15.86	15.86	15.86	15.86
Mag ste	2	2	2	2	2
Total weight (mg/tab)	120	120	120	120	120

NOTE: MS: Montelukast sodium, CP: Crospovidone, Mag Ste: Magnesium stearate

Table 3: Composition of Montelukast sodium Granules and Mini-tablet Filled capsule Systems [GMTFCS]

Formulation code	Composition
GMTFCS- 1	**Granules : SRMT-1:SRMT-2:SRMT-3**
GMTFCS – 2	**Granules : SRMT-1:SRMT-3:SRMT-4**
GMTFCS – 3	**Granules : SRMT-1:SRMT-2:SRMT-5**
GMTFCS – 4	**Granules : SRMT-1:SRMT-3:SRMT-5**

NOTE: The composition of the formulations has been selected based on the results of separate In- vitro dissolution testing of SRMT.

Table 4: Pre-compressional evaluation of the prepared Montelukast sodium SRMT Granules

Tablet code	Angle of repose (degree)	Bulk density (gm/cc) ± SD, n=3	Tapped density (gm/cc)	Carr's index (%), n=3	Hausner's ratio ± SD, n=3
SRMT-1 Granules	25.12 ± 0.14	0.55 ± 0.005	0.64 ± 0.014	19.24 ± 0.16	1.25 ± 0.012
SRMT-2 Granules	23.46 ± 0.18	0.53 ± 0.002	0.66 ± 0.022	23.56 ± 0.18	1.26 ± 0.016
SRMT-3 Granules	24.26 ± 0.28	0.52 ± 0.004	0.67 ± 0.046	17.84 ± 0.12	1.28 ± 0.024
SRMT-4 Granules	22.54 ± 0.42	0.54 ± 0.003	0.63 ± 0.016	15.68 ± 0.22	1.22 ± 0.018
SRMT-5 Granules	27.12 ± 0.12	0.51 ± 0.006	0.62 ± 0.024	18.46 ± 0.08	1.21 ± 0.008

Table 5: Evaluation of Montelukast sodium SRMT

Tablet code	Thickness (±SD), n=6	Diameter (mm) (±SD), n=6	Hardness (kg/cm^2) (±SD), n=6	Friability (%)	Average weight (mg) (±SD), n=20	Drug Content (%) (±SD), n=6
SRMT-1	2.87 ± 0.46	6.3 ± 0.02	3.09 ± 0.04	0.54	120 ± 0.66	98.46 ± 0.46
SRMT-2	2.86 ± 0.062	6.3 ± 0.02	3.14 ± 0.07	0.46	120 ± 1.12	99.08 ± 0.56
SRMT-3	2.97 ± 0.036	6.3 ± 0.04	3.02 ± 0.02	0.58	120 ± 0.92	97.96 ± 0.74
SRMT-4	3.02 ± 0.024	6.3 ± 0.06	2.95 ± 0.12	0.46	120 ± 0.88	98.14 ± 0.86
SRMT-5	2.94 ± 0.072	6.3 ± 0.08	2.85 ± 0.14	0.58	120 ± 0.74	99.98 ± 0.48

Table 6: *In-vitro* release study of sustained-release mini-tablets (SRMT)

Time (hrs)	SRMT-1	SRMT-2	SRMT-3	SRMT-4	SRMT-5
0	0	0	0	0	0
1	23.35	20.18	17.01	10.88	7.71
2	43.75	36.88	30.22	23.88	17.33
3	59.81	54.11	46.29	34.66	26.1
4	76.51	72.28	62.98	48.08	34.03
5	88.34	81.63	74.40	60.02	45.23
6	98.49	93.31	86.76	72.28	53.05
7	--	99.44	94.68	84.12	61.71
8	--	--	99.12	92.68	71.65
9	--	--	--	98.59	82
10	--	--	--	--	91.41
11	--	--	--	--	95.85
12	--	--	--	--	99.02

Table 7: *In-vitro* release study of Granules and Mini-tablets-Filled capsule system (GMTFCS)

Time	GMTFCS-1	GMTFCS-2	GMTFCS-3	GMTFCS-4
0	0	0	0	0
1	37.40	35.85	33.48	29.55
2	51.77	49.39	46.81	41.02
3	67.99	60.34	57.97	50.22
4	78.84	72.02	67.74	60.03
5	87.00	80.91	80.91	68.71
6	92.58	87.41	85.97	74.50
7	97.02	92.68	90.72	80.49
8	99.71	96.61	94.65	87.93
9	--	99.61	97.44	91.55
10	--	--	99.81	93.41
11	--	--	--	96.71
12	--	--	--	99.92

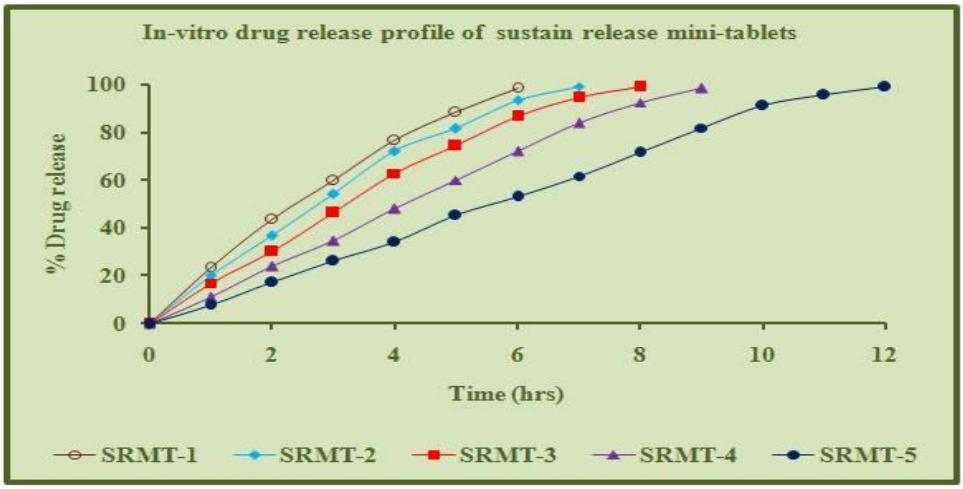

Fig. 1: *In-vitro* drug release profile of Sustained-release mini-tablets (SRMT)

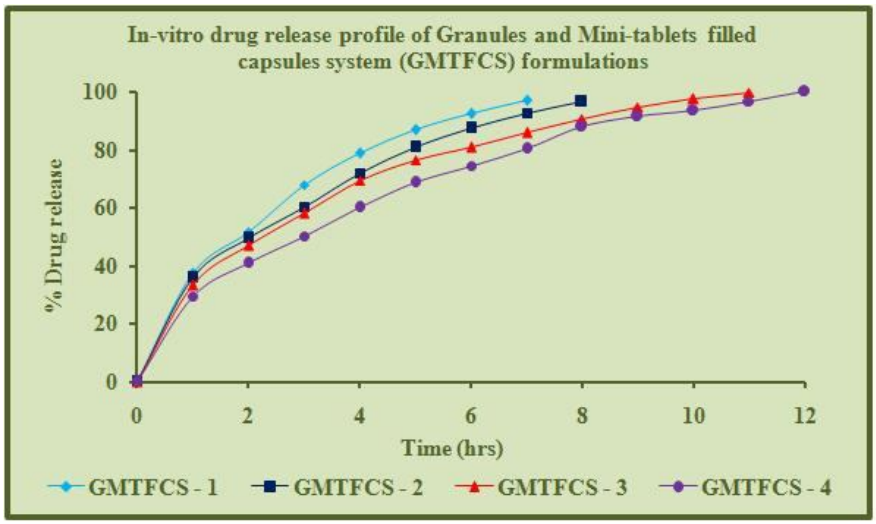

Fig. 2: *In-vitro* drug release profile of Granules and Mini-tablets-Filled capsule system (GMTFCS)

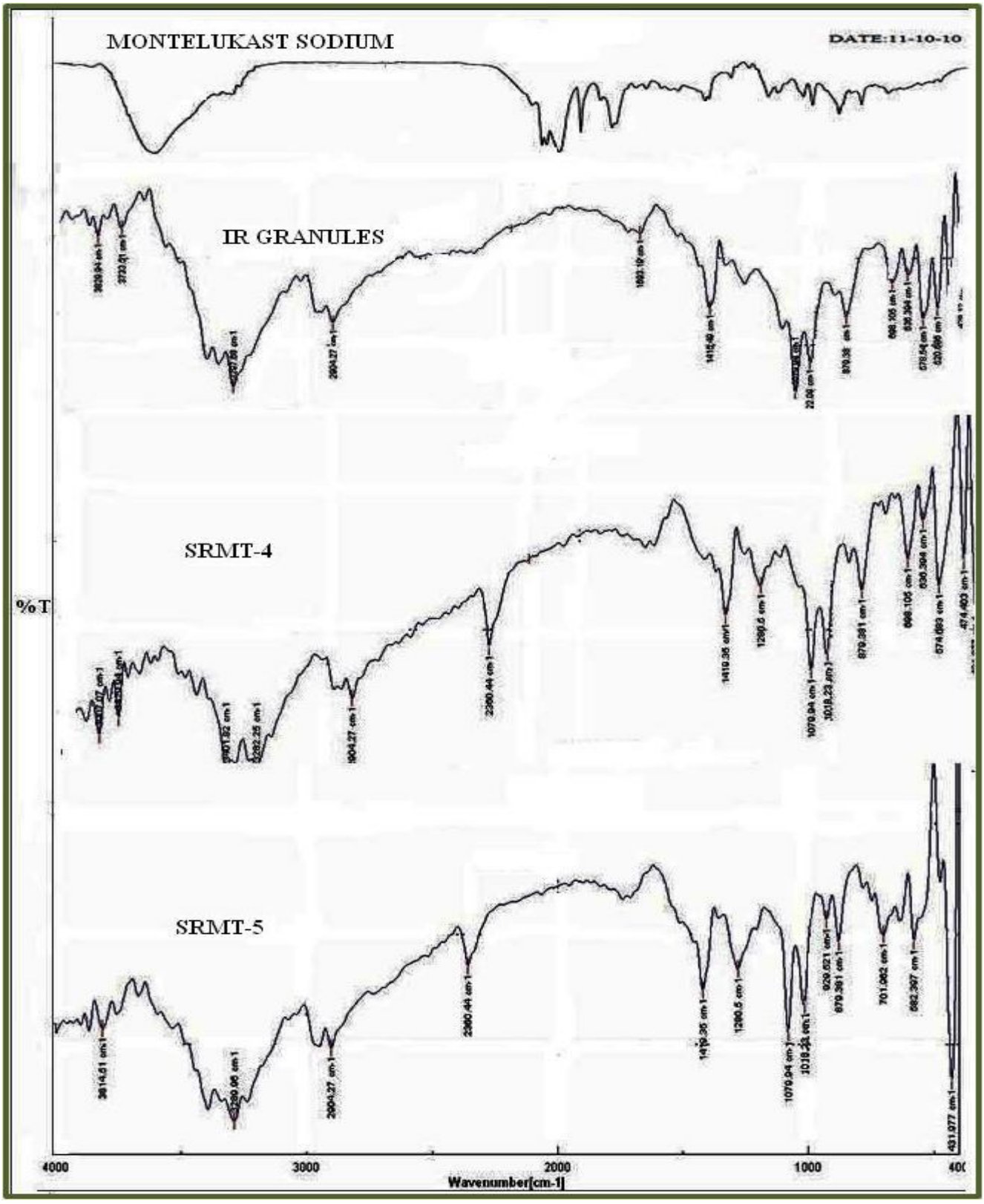

Fig. 4: IR Spectra of pure Montelukast sodium, IR granules and mini-tablet formulations SRMT-3, and SRMT-4

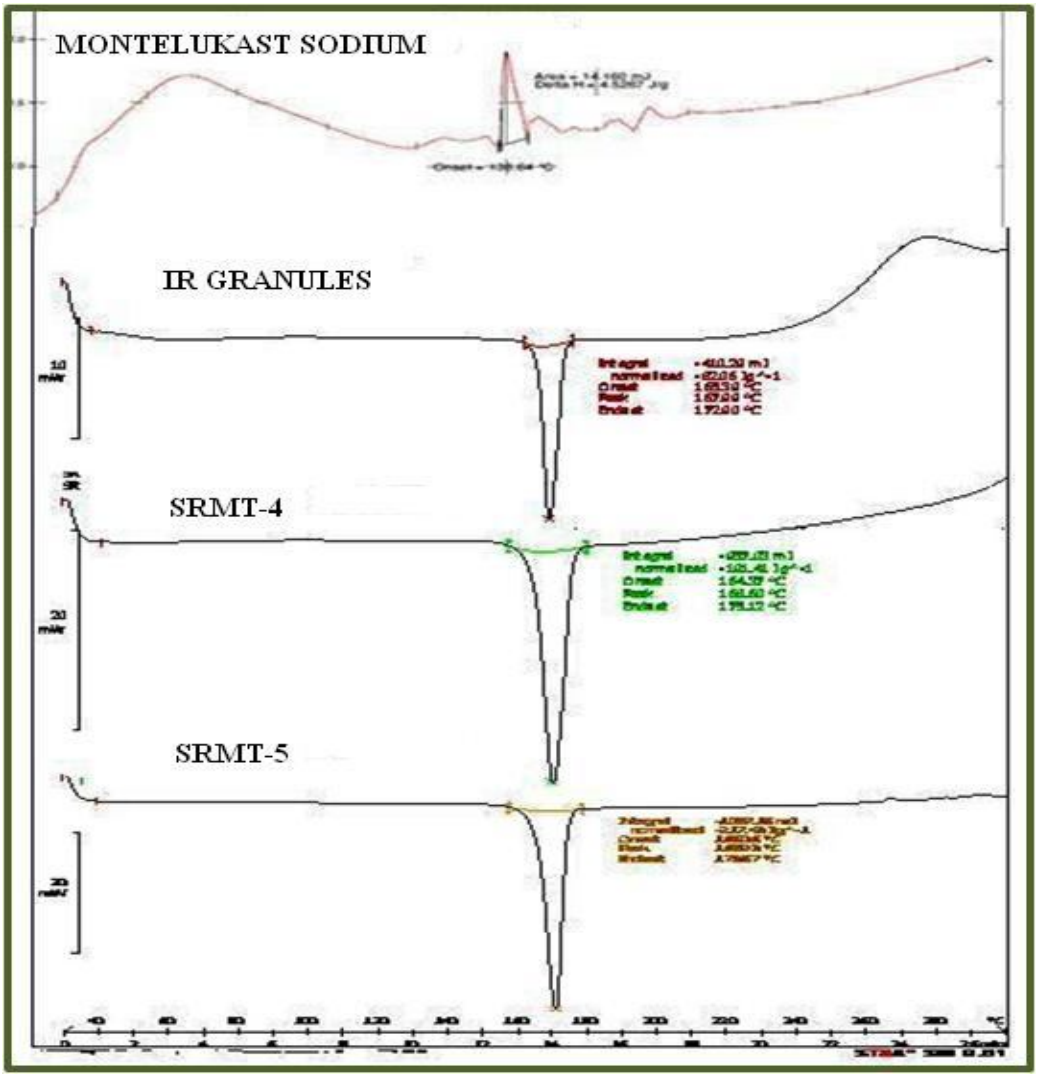

Fig. 5: DSC of pure Montelukast sodium, IR granules mini-tablet formulations SRMT-3 and SRMT-4

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