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Formulation & Evaluation of Orally Disintegrating Tablet of Ondansetron Hydrochloride.

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Abstract

Ondansetron Hcl is a serotonin receptor (5-HT3) antagonist used in the prevention of chemotherapy induced nausea and vomiting. The demand for orally disintegrating tablet has been growing, especially for geriatric and pediatric patients because of swallowing difficulties. In this present study, the bitter taste of Ondansetron Hcl was masked using Tulsion-339 & flavor, also the disintegration time is reduced with using different superdisintegrants . The FTIR studies showed drug and carrier were compatible. These were then compressed into tablets by direct compression method with using different superdisintegrants like Shieffield ODT, Crosspovidone, Pharmaburst-500, Polyplasdone XL-10, Ludiflash. All formulations were evaluated for disintegration time, wetting time, weight variation, percentage friability and in vitro dissolution rate. Formulations F-02 showed disintegration time below 12 sec, wetting time below 10 sec, containing superdisintegrant Shieffield-ODT & Crosspovidone, also shows good sweet taste with no after bitter taste with using tulsion-339 & orange flavour. In vitro dissolution studies of formulations F02 showed more than 95% drug release within 10 minutes. In vitro release profile, disintegration time and wetting time were remaining unchanged after one month when stored at 40 C / 75% RH.

Keywords: Orally disintegrating tablet, in-vitro disintegration time, wetting time, Ondansetron HCL.

Introduction

The concept of MDDDS emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for paediatric and geriatric patients[1]. Administering effervescent tablets/granules and dry syrups involve unavoidable preparation that include the intake of water. Elderly patients cannot chew large pieces of tablets or gums and sometimes experience the bitter or unpleasant taste of the drug in the dosage form if the taste masking coat ruptures during mastication[3].

Ondansetron hydrochloride is serotonin 5-HT3 antagonist useful as antiemetic treatment of emesis. It requires faster onset of action. It is reported to have biological half life of 3 to 5 hour. Hence the present work was aim to develop the mouth dissolving tablet of Ondansetron hydrochloride

Materials & method

Ondansetron Hydrochoride was provided by Shodhana Lab Ltd, Hyderabad. Shieffield ODT was from Kerry Bio-Science, USA. Pharmaburst-500 was from SPI Pharma, Grand Haven MI. Polyplasdone XL-10 was from ANSHUL Life sciences, Mumbai. Ludiflash was from BASF-the chemical company,USA. Tulsion-339 was a gift from THERMAX Ltd, Pune. All other chemicals employed were of analytical grade.

Method of Preparation

Fast dissolving tablets of Ondansetron hydrochloride were prepared using direct compression method incorporating superdisintegrants. The Ondansetron hydrochloride is passed through sieve no.80# & all excipients were passed through sieve no.80#. The Ondansetron hydrochloride equivalent to 4 mg, & excipients were mixed thoroughly.[7] Superdisintegrants, taste masker & other excipients were incorporated in the powder mixture according to each formulation in the table and finally magnesium stearate was added as lubricant. The whole mixture is then passed through sieve no.80 twice. Tablets were prepared using 6.35 mm circular flat-bevelled edge punch of the rotary tablet machine [CIP-Machine12station] at Agio Pharmaceuticals Ltd., Pune. Compression force was kept constant for all

formulations & thickness of the tablet was kept in 2.6±0.3mm.[8] All the formulations were given in table no 2.

Evaluation Parameters

Evaluation of Powder blend

The prepared blends were evaluated for following properties-

Angle of repose:[19]

The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The angle of repose is calculated as,

$$\tan\theta = h/r$$

Therefore, $\theta = \tan^{-1}(h/r)$

Where, θ = Angle of Repose
h = Pile height
r = Radius of pile

Bulk density:[19]

The powder sample, 25 g was accurately weighed and filled in a 100 ml graduated cylinder and the powder was leveled and the unsettled volume, (Vo) was noted. The bulk density was calculated as,

$$\text{Bulk density } (\rho_o) = M/Vo$$

Where, ρ_0 = Bulk density
M = Mass of powder taken
V_o = Apparent unstirred volume

Tapped density:[19]

The tapped density was determined by following formula

$$\text{Tapped density } (\rho_t) = M / V_t$$

Where, ρ_t = Tapped density
M = Weight of granules
V_t = Tapped volume of granules in cm^3

Carr's index: [19]

It was determined from the formula:

$$C = \frac{\rho_t - \rho_0}{\rho_t} \times 1$$

Where, ρ_t = Tapped density
ρ_0 = Bulk density
C = Compressibility index

Hausner's ratio: [19]

It can be calculated as

$$\text{Hausner's ratio} = \rho_t / \rho_0$$

Where, ρ_t = Tapped density
ρ_0 = Bulk density

Results of above tests were summarized in table no Table No. 2.

Evaluation of orally disintegrating tablet

Physical evaluation:

All the batches of prepared tablets were evaluated for various following parameters-

Dimension[19]:-

The thickness and diameter of the tablets was determined using a Vernier caliper. Five tablets from each type of formulation were used and average values were calculated.

Hardness[19]:-

Hardness was measured using the Monsanto hardness tester.

Friability[18]:-

Roche Friabilator was used for the purpose, 10 tablets were weighed and placed in the Roche friabilator test apparatus, the tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 evolutions the tablet were de-dusted and weighted again. The friability was determined as, (IP, 2007)

$$\% \text{ Friability} = 1 - \left(\frac{\text{Weight of tablet after test}}{\text{Weight of tablet before test}} \right) 100$$

Weight variation test[18]:-

According to method given in IP, weight variation test is done by 20 tablets were selected randomly. By weighing tablets individually; calculating the average weight and comparing the individual tablet weight to average weight variation tolerance .

Wetting time[17]:-

A piece of tissue paper folded twice containing amaranth powder on the upper surface was placed in a small Petri dish (ID =6.5 cm) containing 6 ml of distilled water, a tablet was put on the paper and the time required for formation of pink color was measured as wetting time. Three trials for each batch were performed and standard deviation was also determined

Water absorption ratio[17]:-

A piece of tissue paper folded twice was placed in a small petri dish containing 6ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then weighed[16]

Water absorption ratio R was determined using following equation:

$$R = \left\{ \frac{(Wb - Wa)}{Wa} \right\} 100$$

Where, Wa = Weight of the tablet after wetting
Wb = Weight of the tablet before wetting

Uniformity of drug content[17]:-

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 10 mg of Ondansetron hydrochloride was dissolved in 100 ml of 0.1N hydrochloride, filtered diluted suitably and analyzed for uniformity of content at 310 nm using UV-Visible spectrophotometer. (IP, 2007; Jha, *et al* 2008)

Content uniformity was calculated using formula:

$$\% \text{ Purity} = 10\ C\ (Au / As)$$

Where, C – Concentration
Au and As – Absorbance of unknown and standard respectively

Disintegration time[18]:-

Initially, the disintegration time for fast dissolving tablets was measured using the conventional test for tablets as described in the Pharmacopoeia. Tablets were placed in the disintegration tubes and time required for complete disintegration, that is without leaving any residues on the screen was recorded as disintegration time.

In-vitro dissolution studies:- [11 12]:

Tablets were placed in USP type II dissolution test apparatus which was maintained at the parameters given in table no 1. The sample ,10 ml, was withdraw from the each basket at the time interval of 2 minutes. The sample was spectroscopically analysed at 310 nm using UV-Visible spectrophotometer (Labindia 3000+). The drug released from the tablets was calculated using PCP Disso. software. The drug release from the tablets was summarized in table no 2.

Stability study

Accelerated stability studies (AST) was carried for optimized batch F 02 exposing it to 45 C/75% RH for 7, 14, 21 and 28 days as per ICH guidelines. The formulation was analyzed on 7 th, 14 th,21st and 28 th days for various parameters to observed the physical and chemical changes as given in table no 5. FT-IR Spectroscopy and DSC study was carried out for the formulation on 0 day and on 28th day.

Result and discussion

All the evaluation parameters like diamention, hardness, friability, disintegration time,wetting time, water absorption ratio of all the formulation were found to be in prescribed limit(table 4A,4B)The drug release was found above 44 % after 2 minutes for all the formulations, for all the formulations we were used superdisintegrants for getting maximum drug release & taste masker to hide bitter taste Formulation batch no. F 02 releases 99.25 % of drug after 10 minutes (Table no-4), while formulation batch no. F, 01 released only 97 of drug after 10 minutes, which contains Sheffield ODT, crosspovidone as superdisintegrant & Tulsion 339,orange flavor as taste masker

Results of the drug interaction studies suggest that all the studied excipients are compatible with Ondansetron hydrochloride

In present study it is found that there is no change in the transition temperature (Exothermic change) between drug & formulation-02

From the above formulations the optimum batch found to be batch containing Shieffield ODT and Crospovidone (CP) as (i.e. formulation F 02), depending upon the factors such as less friability, high water absorption ratio, less disintegration time[13 14]. (Figure1, 2, 3)

Conclusion

The fast dissolving tablets of Ondansetron hydrochloride were more palatable, also helpful to the patients having persistant vomiting which can lead to patient discomfort with or unwillingness to swallow the available oral tablet and associated water. Hence, at the end of this investigation it can be cocluded that ODT of Ondansetron hydrochloride was successfully prepared by conventional direct compression method using different superdisintegrants and the objectives of this study are achieved and optimize batch is F02.

Acknowledgement

Shodhana Lab Ltd, Hyderabad. Kerry Bio-Science, USA. SPI Pharma, Grand Haven MI. ANSHUL Life sciences, Mumbai. BASF-the chemical company,USA. THERMAX Ltd, Pune is gratefully acknowledged for providing the gift samples Ondansetron Hydrochoride, Shieffield ODT, Pharmaburst-500, Polyplasdone XL-10, Ludiflash, Tulsion-339 respectively. All other chemicals employed were of analytical grade.

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Table No. 1: Dissolution test parameters

Sr. No	Parameter	Spécifications
1	Apparatus	USP dissolution apparatus (Type II)
2	Speed	50 RPM
3	Temperature	37± 0.5 °C
4	Dissolution medium	0.1 N hydrochloric acid
5	Volume of medium	500 ml
6	Sampling interval	2 min

Table No.2 : Formulation of MDDDS

ING. / F.C.	F1	F2	F3	F4	F5	F6	F7	F8
Ond. hydrochloride (mg)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Sheffield ODT	50	52	___	___	---	----	60	…
Crosspovidone	9	10	5	5	---	----	----	60
Pharmaburst500	....	**.....**	60	65	---	-----	----	…
PolyplasdoneXL10*	….	___	…..	___	30	35	….	----
Ludiflash	…..	___	…..	___	30	25	…..	-----
Tulsion339	14	12	…..	___	15	15	15	15
Orange fl.	14	13	15	10	5	5	10	10
Aspartame	3	3	5	5	5	5	5	5
Peppermint.fl.	….	___	__	----	5	5	…	---
Sucralose	…..	___	5	5	--	….	…	---
Lake sunset yellow	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mg.Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Sod.lauryl sulphate	2	2	2	2	2	2	2	2
Total(mg)	100	100	100	100	100	100	100	100

Table No. 3: Evaluation of powder blend

Parameters / Formulations	Angle of Repose (^{0}) ±SD	Bulk Density (g/ml) ±SD	Tapped Density (g/ml) ±SD	Carr's Index (%)±SD	Hausner's Ratio ±SD
F 01	26.45 ±0.50	0.57 ±0.031	0.63 ±0.040	11.67 ±0.73	1.10 ±0.010
F 02	27.87 ±0.64	0.49 ±0.032	0.69 ±0.022	14.87 ±0.60	1.17 ±0.008
F 03	25.69 ±0.55	0.58 ±0.018	0.64 ±0.020	13.72 ±0.27	1.09 ±0.003
F 04	26.65 ±0.39	0.55 ±0.024	0.62 ±0.024	15.71 ±0.71	1.13 ±0.009
F 05	22.32 ±0.78	0.57 ±0.037	0.67 ±0.051	15.31 ±0.99	1.18 ±0.014
F 06	28.71 ±0.59	0.54 ±0.025	0.65 ±0.036	16.81 ±0.77	1.20 ±0.011
F 07	29.93 ±0.46	0.59 ±0.024	0.66 ±0.032	12.96 ±0.49	1.13 ±0.009
F 08	26.53 ±0.32	0.53 ±0.012	0.59 ±0.012	12.20 ±0.34	1.11 ±0.001

Table No.4A: Evaluation of Formulated Tablets

Parameters / Formulations	Thickness (mm) ± SD	Hardness (kg/cm^2)	Weight Variation (mg)	% Friability ± SD
F 01	2.6±0.03	2-3	100±7.5	0.003±0.21
F 02	2.6±0.03	2-3	100±7.5	Nil
F 03	2.6±0.03	2-3	100±7.5	0.510±0.30
F 04	2.6±0.03	2-3	100±7.5	0.427±0.32
F 05	2.6±0.03	2-3	100±7.5	0.374±0.64
F 06	2.6±0.03	2-3	100±7.5	0.343±0.51
F 07	2.6±0.03	2-3	100±7.5	0.250±0.36
F 08	2.6±0.03	2-3	100±7.5	0.375±0.35

Table No.4B: Evaluation of Formulated Tablets

Parameters / Formulations	Content Uniformity Mean(%) ±SD	Wetting time (Sec) Mean ± SD	Water Absorption Ratio Mean ± SD	Disintegration Time (Sec) Mean ± SD
F01	97.79±0.73	10±0.70	99.50±0.71	12±2
F 02	99.27±0.63	10±0.50	109.34±0.81	11±2
F 03	98.63±0.98	20±0.40	87.75±0.39	32±3
F 04	99.55±0.35	19±0.76	91.58±0.56	28±3
F 05	96.77±0.55	13±0.75	87.81±0.62	18±5
F 06	97.81±0.44	13±0.73	88.44±0.78	19±2
F 07	98.96±0.87	15±0.79	95.65±0.91	20±4
F 08	97.99±0.14	15±0.70	92.10±0.59	20±2

Table No.4: Results of in-vitro dissolution study of F 02 formulation

Sr no / F	Time	F1	F2	F3	F4	F5	F6	F7	F8
1	0	0.000 ± 0.0	0.000 ± 0.0	0.000 ± 0.0	0.000 ± 0.0	0.000 ± 0.0	0.000 ± 0.0	0.000 ± 0.0	0.000 ± 0.0
2	2	55.38 ± 0.75	54.18 ± 0.99	52.16 ± 0.25	52.69 ± 0.65	45.34 ± 0.41	54.42 ± 0.56	55.67 ± 0.55	46.51 ± 0.65
3	4	63.99 ± 0.29	69.85 ± 0.31	65.86 ± 0.53	65.12 ± 0.47	60.49 ± 0.83	66.87 ± 0.63	65.44 ± 0.59	62.45 ± 0.91
4	6	79.12 ± 0.65	80.49 ± 0.54	74.97 ± 0.87	79.16 ± 0.61	78.15 ± 0.74	74.43 ± 0.43	76.56 ± 0.95	77.86 ± 0.91
5	8	89.2 ± 0.55	90.23 ± 0.67	82.67 ± 0.52	86.45 ± 0.38	85.25 ± 0.82	86.86 ± 0.28	83.69 ± 0.32	85.20 ± 0.86
6	10	97.20 ± 0.12	99.25 ± 0.3	89.49 ± 0.67	91.52 ± 0.85	95.79 ± 0.86	96.27 ± 0.65	94.61 ± 0.49	93.64 ± 0.45

Table No.5**:** *Evaluation Parameter of Stability Batch of F 02*

	Days			
	7	14	21	28
Hardness(Kg/cm^2)	2.-3	2-3	2-3	2-3
Drug Content (%)	99.24 ± 0.47	98.90 ± 0.59	98.67 ± 0.35	98.41 ± 0.74
***In-vitro* disintegration time**	11.63 ± 0.88	11.37 ± 0.39	11.19 ± 0.67	11.85 ± 0.44
Max drug release	98.94 ± 0.92	98.51 ± 0.75	98.22 ± 0.39	98.01± 0.47

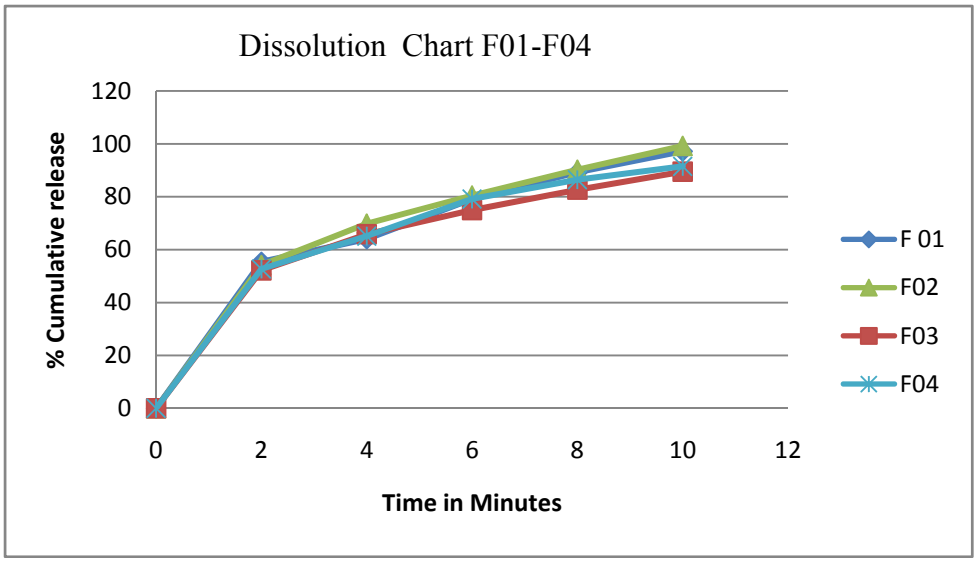

Figure. 1: Dissolution profile of formulation F 01, F 02, F 03, F 04,

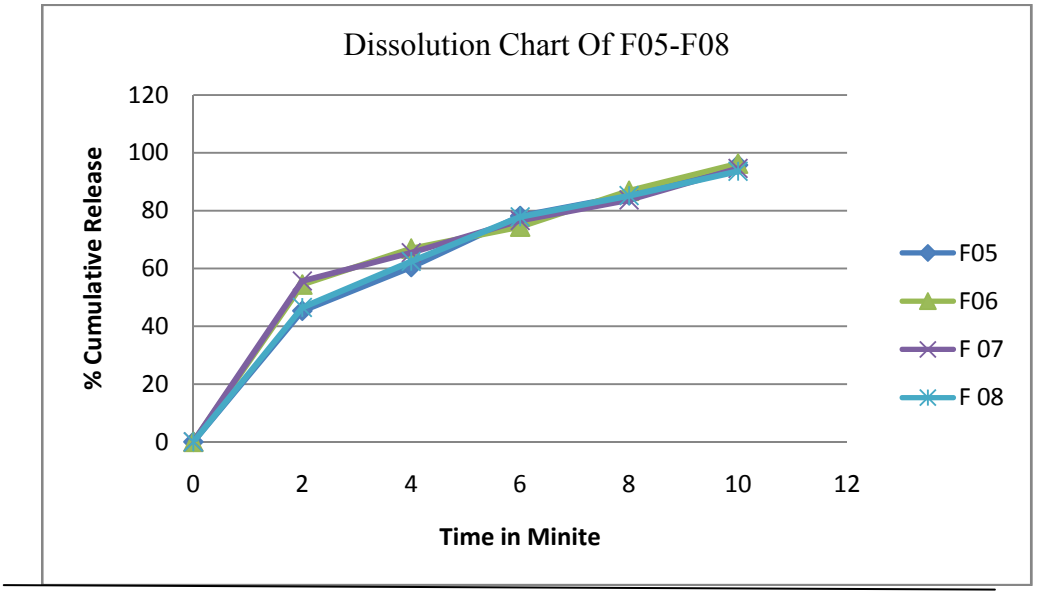

Figure 2: *Dissolution profile of formulation F 05, F 06, F 07, F 08*

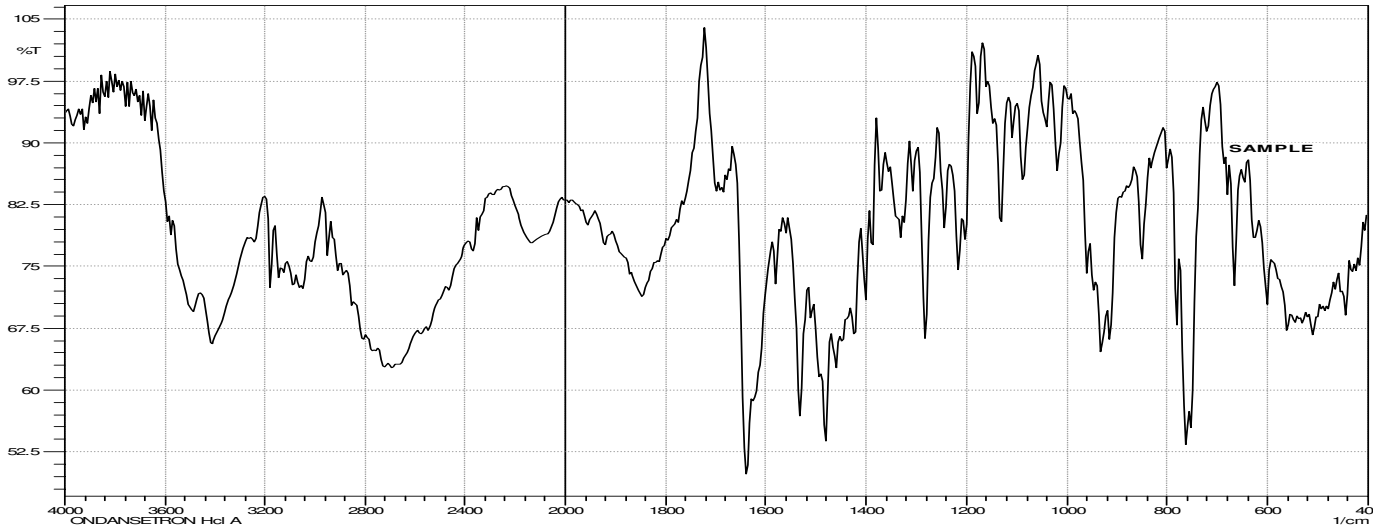

Figure 3: *FTIR Spectra of Pure Drug Ondansetron hydrochloride (Sample)*

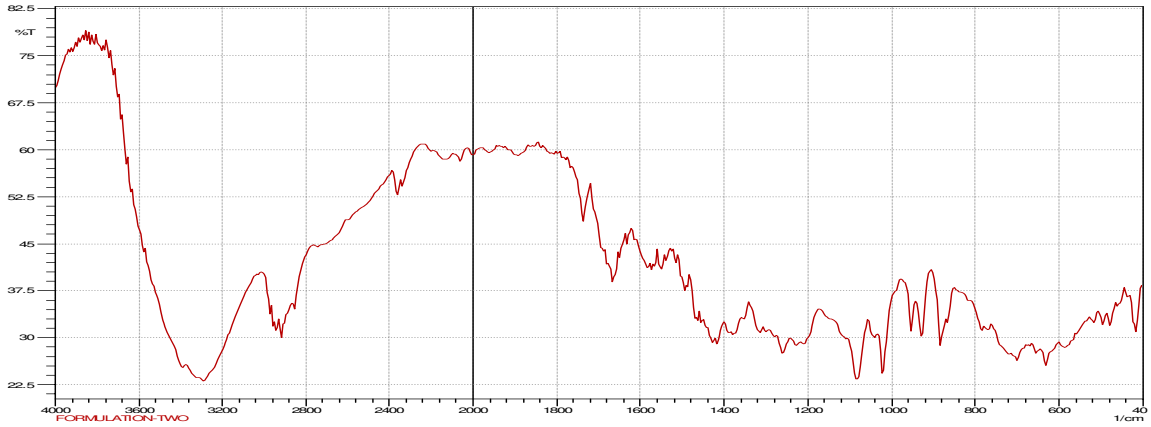

Figure 4: *FTIR Spectra of R 02 Formulation (Tablet)*

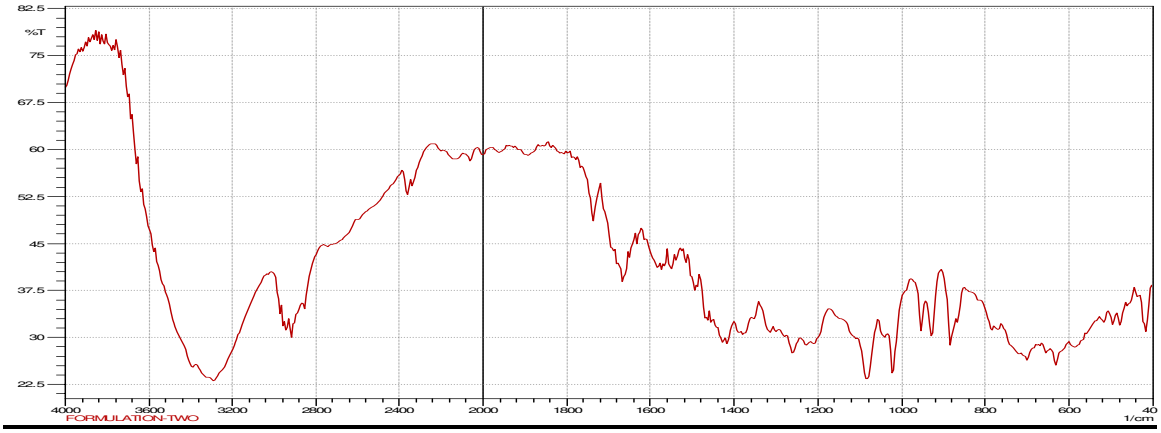

Figure 5: *FTIR Spectra of R 02 Formulation (Tablet)of stability batch*

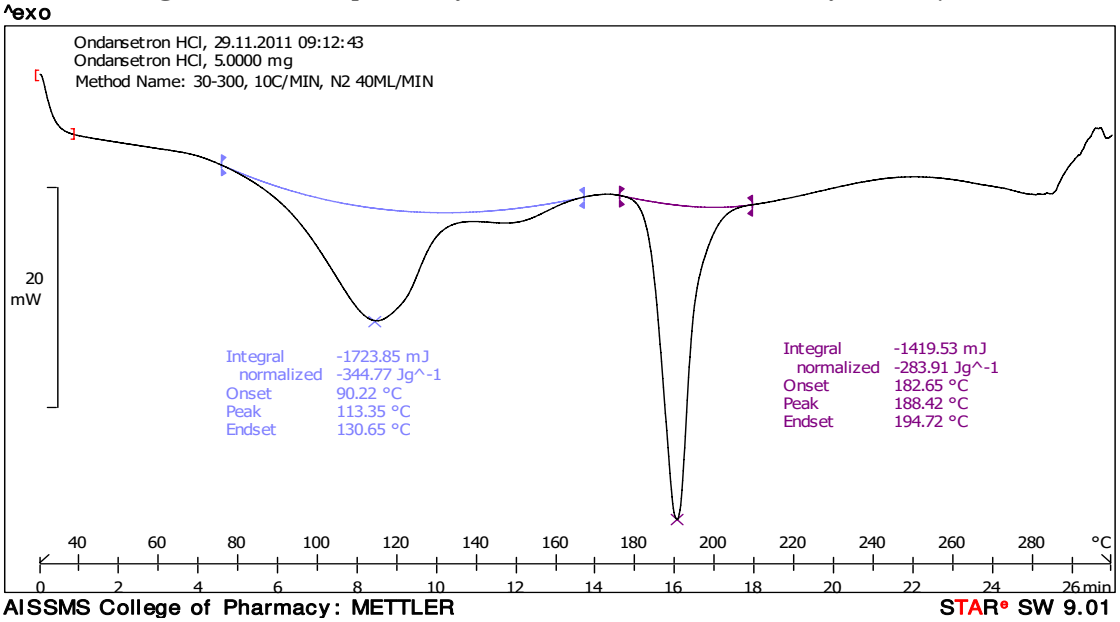

Figure 6A: *DSC OF Drug Ondansetron hydrochloride*

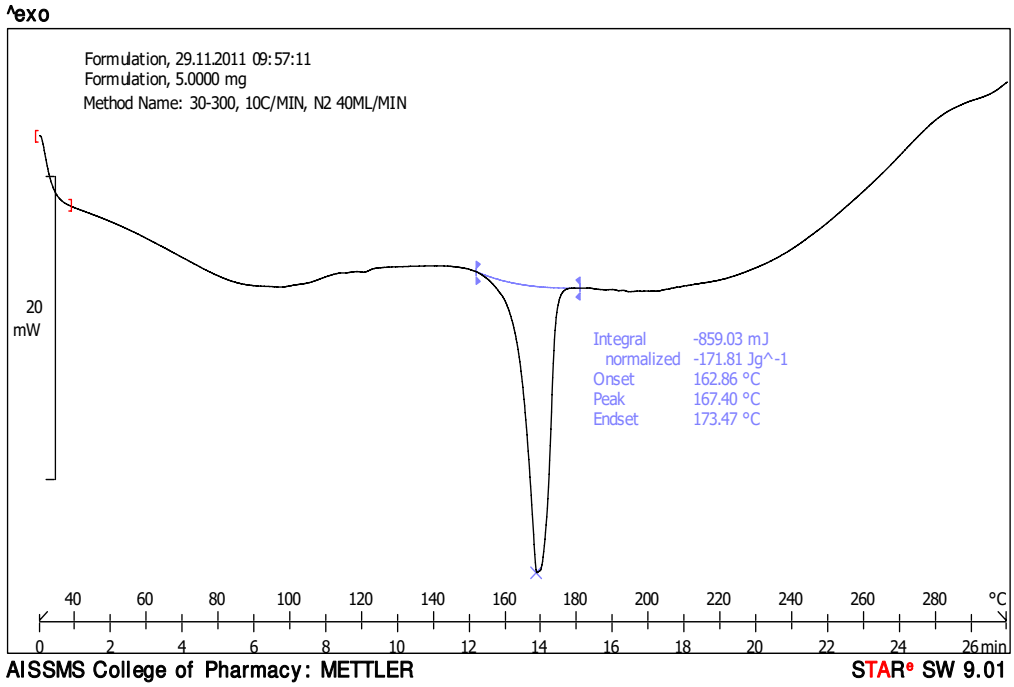

Figure 6B: *DSC OF Formulation 02 (Tablet)*

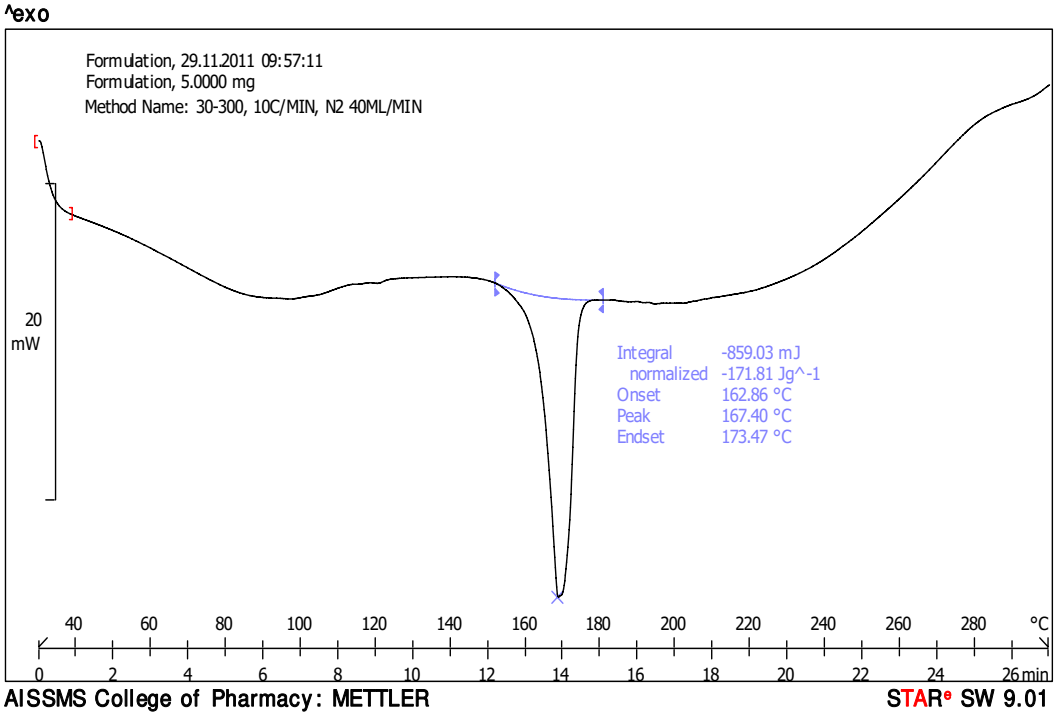

Figure 7: *DSC OF Formulation 02 (Tablet) of stability batch*