

FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF ONDANSETRON HYDROCHLORIDE

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Summary

The objective of the present investigation was to prepare mouth dissolving tablets of ondansetron HCl by direct compression method using different super disintegrants, viz., croscarmellose sodium, crospovidone and sodium starch glycolate by different methods physical mixtures, solid dispersions and melt method. Mouth dissolving tablet is the fast growing and highly accepted drug delivery system, convenience of self administration, compactness and easy manufacturing. Ondansetron HCl is a highly selective and potent antagonist of 5-hydroxytryptamine at 5HT₃ receptors in the gastrointestinal tract where it blocks both sites of serotonin induced nausea and vomiting (emesis). The tablets were examined for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The prepared tablets were evaluated for thickness, hardness, friability, and weight variation, content uniformity, wetting time, water absorption ratio, *in-vitro* dispersion time, dissolution studies and FTIR studies. Twelve formulations F1 to F12 were prepared with three super disintegrants with different concentration. The optimum formulation was chosen and their optimum results were found to be in close agreement with experimental finding. Among three super disintegrants, crospovidone emerged as overall best superdisintegrant and formulation F9 emerged as overall best formulation. Short-term stability studies on the formulations indicated no significant changes in the drug content and *in vitro* dispersion time ($p < 0.05$).

Keywords: Mouth dissolving tablets, super disintegrants, ondansetron, direct compression.

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Introduction

Most of the oral pharmaceutical dosage form like conventional tablets and capsules are formulated but it was difficult to swallow for elderly and children. This problem is also applicable to active working or travelling people who do not have ready access to water¹. Recent advances in novel drug delivery system aims to provide rational drug therapy by enhanced safety and efficacy of drug molecule by formulating convenient dosage form to administration². One such approach is mouth dissolving tablets (MDTs). A mouth dissolving tablet is a solid dosage form that disintegrates and dissolves in mouth without water within 60 seconds or less³. The various technologies used to prepare MDTs include freeze drying and sublimation⁴. Ondansetron Hydrochloride is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single 8mg tablet, is approximately 56%. In the case of poorly water soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs due to erratic and incomplete absorption from GIT. Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs, in general, include micronization, the use of surfactant, and the formation of solid dispersions. Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and incase of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance. To overcome these drawbacks, fast dissolving tablets (FDTs) or mouth dissolving tablets; (MDTs) has emerged as alternative oral dosage forms. These are novel types; of tablets that disintegrate/dissolve/ disperse in saliva within few seconds. The basic approach used in development of FDT is the use of superdisintegrant which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva drug that is subject to first pass metabolism is reduced as compared to standard tablets.⁵

The commonly used super disintegrants are croscarmellose sodium, L-hydroxypropylcellulose, crospovidone and sodium starch glycolate⁶. In many mouth dissolving tablet technologies based on direct compression, the addition of super disintegrants principally affects the rate of disintegration and hence dissolution and also effervescent agent also further hastens the process of disintegration. Ondansetron HCl is a highly selective and potent antagonist of 5-hydroxytryptamine at 5HT₃ receptors in the gastrointestinal tract where it blocks both sites of serotonin induced nausea and vomiting (emesis). It was selected as drug candidate, since it is not available in such dosage form.⁵ Aim of the present study was to develop mouth dissolving tablets of Ondansetron HCl by simple and cost effective direct compression method using different super disintegrants, croscarmellose sodium, crospovidone and sodium starch glycolate at different concentrations with the help of different preparation like physical mixtures, solid dispersions and melt method. The prepared tablets were evaluated for *in vitro* dispersion time, hardness, friability, wetting time and *in vitro* drug release.

Material and Method

Ondansetron HCl(OSH) was gift sample from Aventis Pharma, Gujarat. Sodium starch glycolate, croscarmellose sodium and crospovidone were obtained as gift sample from AET Laboratories Hyderabad. Microcrystallinecellulose were gift sample from LOBA Chemical Pvt. Ltd., Mumbai. All other chemicals used were of analytical reagent grade.

Preparation of Physical Mixtures

OSH and excipient (Crospovidone, Croscarmellose sodium, Sodium starch glycolate) were passed through 100 mesh and then accurately weighed in a 1:3 ratio (Table 1). They were mixed well in a mortar and sifted through 80 mesh.

Preparation of Solid Dispersions

I Solvent evaporation Method

Solid dispersions containing drug (OSH) and excipient in the proportion of 1:3 were prepared employing crospovidone, croscarmellose sodium, sodium starch glycolate as excipients. OSH was dissolved in alcohol to a clear solution. The OSH solution was then poured onto the excipient, put in a mortar, and mixed thoroughly. The wet solid mixture was dried at 60°C for 4 hr in hot air oven and the coprecipitate (coevaporated products, COE) obtained was powdered in a mortar and passed through a 80 mesh sieve and stored in a desiccator at room temperature for 24 hours.

Tablet 1 Formulation of Ondasetron HCl Mouth Dissolving Tablets by Direct Compression Method

Ingredients (mg)*	F1-P	F2-S	F3-M	F4-P	F5-S	F6-M	F7-P	F8-S	F9-M
Ondasetron hydrochloride	8	8	8	8	8	8	8	8	8
Croscarmellose sodium	8	8	8	--	--	--	--	--	--
Sodium starch glycolate	--	--	--	8	8	8	--	--	--
Crospovidone	--	--	--	--	--	--	8	8	8
Microcrystalline cellulose 102	92	92	92	92	92	92	92	92	92
Aspartame	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3	3	3	3	3
Total weight	120	120	120	120	120	120	120	120	120

* All the quantities expressed are in mg/tablet. P = Physical Mixtures, S = Solvent evaporation Method and M = Melt Method

II Melt Method

Solid dispersions containing drug (OSH) and excipient (croscopovidone, croscarmellose sodium, sodium starch glycolate) in the proportion of 1:3 were prepared by melt method. In the melt method the drug was incorporated, under stirring, into the melted carrier ($70\pm 5^\circ\text{C}$), heating until a homogeneous melt was obtained and then it was kept in an ice bath for sudden cooling (cofused products, COF). The mass was kept in the desiccator for complete drying. The solidified mass was scrapped, crushed, pulverized, and passed through 80 mesh.

Preparation of mouth dissolving tablets

Direct Compression Method

Mannitol (pearlitol SD200), MCC (avicel PH 101) and aspartame were passed through 60 mesh before use. The excipients and Drug (as such or in 1:3 Solid dispersion or in 1:3 Physical mixtures with CP) were then blended together by tumbling for 10 min. The blend was lubricated with 1% magnesium stearate and 2% talc. The final blend was mixed for 5 to 7 min and compressed in to tablets using a rotary tablet machine. The compositions are shown in Table 1

Characterization of Solid Dispersion

Transform Infrared Spectroscopy studies

FTIR spectra of the pure drug, excipients and some selected samples prepared by solvent method of Solid dispersion were obtained on a Perkin-Elmer 1600 FTIR spectrometer (Perkin elmer, spectrum GX FTIR system USA). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1} .

X-ray Diffraction studies

XRD patterns of pure drug with excipients and some selected samples prepared by solvent method of Solid dispersion were obtained using a powder diffractometer (X'pert, MP. Philips). Powdered samples were studied by placing a thin layer of powder in conventional cavity mounts. The sample scans were started at 3.025° angle at 2θ to 99.975° end angle. The source was X-ray tube with Cu target operated at 2 kW X-ray power that generated $k\alpha$ radiation and detector was Xe-filled counteract or propotional detector.

Differential Scanning Calorimetry studies

The DSC thermograms of pure drug, excipients and some selected samples prepared by solvent method of Solid dispersion were recorded on a DSC (Perkin elmer Instruments, Pyris-1DSC). The samples were weighed and hermetically sealed in aluminium pans. Thermal Analysis System instrument Pyris-1 DSC with intracooler, a refrigerated cooling system, was used. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The system was purged with nitrogen gas at a flow rate of 80 mL/min . Initially a sample were held at 50°C for 1 min and after the heating was performed from 50°C - 300°C at a rate of 10°C/min .

Evaluation of Blends

Angle of repose

Angle of repose was determined by using funnel method⁶. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and the angle of repose (Θ) was calculated using the formula.

$$\Theta = \tan^{-1} (h / r)$$

Bulk density

Apparent bulk density (p_b) was determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula⁷.

$$p_b = M / V_b$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (p_t) was calculated by using formula.

$$p_t = M / V_t$$

Compressibility index

The simplest way for measuring of free flow of powder was compressibility, a indication of the ease with which a material can be induced to flow was given by compressibility index (I).⁷

$$I = (V_0 - V_t / V_0) 100$$

Where, v_0 is the bulk volume and v_t is tapped volume.

Hausner's ratio

Hausner's ratio was an indirect index of ease of powder flow. It was calculated by the following method

$$\text{Hausner ratio} = p_t / p_d$$

Where, p_t is tapped density and p_d is bulk density lower hausner's ratio (< 1.25) indicates better flow properties than higher ones (> 1.25).⁸

Evaluation of Tablets**Weight variation**

Twenty tablets were selected at random and weighted individually. The individual weights were compared with average weight for determination of weight variation.

Friability

Friability of the tablets was determined by using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were deducted using a soft muslin cloth and reweighed. The friability (f) was given by the formula.

$$F = (1 - W_0 / W) 100$$

Where, W_0 is weight of the tablets before and W is weight of the tablets after test.

Hardness

Hardness was measured by using Monsanto hardness tester.⁷

Thickness

Thickness was measured by using digital Vernier calipers.

Wetting time and water absorption ratio

The method reported by Yunixia *et al*⁹ was following to measure the tablet wetting time. A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a Petridish containing 6 mL of simulated saliva pH 10, a tablet was put on the paper ,the time required for complete wetting was measured. The wetted tablet was taken and weighed. Water absorption ratio (R) was determined by using following equation

$$R = 100 \times (W_a - W_b) / W_b$$

Where W_b is weight of tablet before water absorption and W_a is weight of tablet after water absorption.

Content uniformity

Ten tablets were weighed and powdered. The powder equivalent to 12.5 mg of Ondasetron content was determined by measuring the absorbance at 265 nm after appropriate dilution with methanol. The drug content was calculated as an average of three determinations.

***In vitro* dispersion time**

One tablet was placed in a beaker containing 10 mL of pH 6.8 phosphate buffer at $37 \pm 0.5^\circ\text{C}$ and time required for complete dispersion was determined.

***In vitro* dissolution study**

In vitro dissolution of Ondasetron mouth dissolving tablets was studied in USP XXIII type-2 dissolution apparatus (Electrolab, Model- TDT- 08L) employing a paddle stirrer at 50 rpm using 500 mL of pH 6.8 phosphate buffer at $37 \pm 0.5^\circ\text{C}$ as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium (5 mL) were withdrawn at specific intervals of time and analyzed for drug content by measuring the absorbance at 310 nm. The volume withdrawn at each time interval was replaced with fresh quantity of the dissolution medium. Cumulative percent of drug released was calculated and plotted against time. The data for dissolution studies were shown in table-4.

Short term stability studies

Short-term stability studies on the promising formulations F9 were carried out by storing the tablets at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH over a 3 month period. At intervals of 1month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

Results and Discussion

Nine formulations of ondansetron HCl were prepared by direct compression method with different superdisintegrant, croscarmellose sodium, sodium starch glycolate and crospovidone with microcrystalline cellulose and directly compressible mannitol was used as diluents to enhance mouth feel. The slight bitter taste of the drug has been masked by using aspartame. A total of nine formulations were designed by three methods of preparations, physical mixtures, solvent evaporation method, and melt method. The powder blend was evaluated the physical properties such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio were tabulated in Table 2. The angle of repose between 28 and 31, this indicates passable flowability, the percentage compressibility index and hausner's ratio were within the limits.

Table 2 Evaluation of Ondansetron Mouth Dissolving Tablet Blend

Batches	Angle of repose	Bulk density	Tapped density	Hausner ratio	% compressibility index
F1	30° 68''	0.49	0.46	0.061	6.122
F2	30° 27''	0.46	0.43	0.065	6.522
F3	30° 54''	0.41	0.38	0.073	7.317
F4	29° 51''	0.46	0.42	0.087	8.696
F5	28° 34''	0.45	0.42	0.067	6.667
F6	31° 91''	0.48	0.46	0.042	4.167
F7	28° 21''	0.46	0.43	0.065	6.522
F8	30° 49''	0.44	0.42	0.045	4.545
F9	28° 58''	0.48	0.46	0.042	4.167

The prepared tablets were evaluated for hardness, friability, thickness, weight variation, content uniformity were shown in Table 3. The drug content was found to be in the range of 98 to 100 (acceptable limits) and the hardness of the tablets was found to be 2.7 to 3.6 kg/cm² were tabulated in Table 3. Friability below 1% was indicating good mechanical resistance of tablets. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in the presence of little amount of water were also found within the limits.

TABLE 3: EVALUATION OF ONDANSETRON ORODISPERSIBLE TABLET

Formulations	Hardness Kg/cm ² ±SD	Friability (%)	Thickness (mm)	Content uniformity (%) ±SD	Wetting time (s)	<i>In vitro</i> dispersion time (s) ±SD	Water absorption ratio (%)
F1	2.76±0.02	0.96	2.48±0.02	98.46±0.6	92±0.81	54±1.24	66.3±0.54
F2	3.66±0.07	0.89	2.44±0.02	98.86±0.6	63±0.21	40±1.34	71.3±0.56
F3	3.20±0.11	0.69	2.51±0.04	99.47±1.8	42±0.24	38±1.32	77.4±0.45
F4	2.88±0.05	0.94	2.49±0.02	99.75±1.6	55±0.25	53±1.26	74.6±0.64
F5	2.68±0.01	0.64	2.55±0.06	99.86±0.9	30±0.85	54±1.26	72.1±0.88

F6	2.70±0.12	0.64	2.48±0.05	100.46±0.9	34±0.92	46±1.04	78.3±0.78
F7	2.82±0.15	0.73	2.49±0.08	98.46±0.7	63±1.12	31±1.25	67.3±0.24
F8	2.86±0.01	0.89	2.58±0.06	98.46±1.5	35±0.13	38±1.24	72.0±0.45
F9	2.80±0.03	0.78	2.55±0.03	99.25±1.2	68±1.24	25±0.98	28.4±0.65

*Average of three determinations

In vitro dispersion test was done for all the formulation. Tablet disintegration was affected by the wicking and swelling of the disintegrants from the nine formulations F9 (crospovidone by melt method) shown less disintegration time, 25 seconds when compared with others super disintegrants. Water absorption ratio for F9 was 28.40% it shows good water absorption capacity. *In vitro* drug release studies of ondansetron prepared tablets F1 to F9 using different super disintegrating agents by different concentrations. The drug release for the formulation F1, F2 and F3 using different method with croscarmellose sodium, at the end of the 15 minutes the drug release was found to be 96%, 96% and 95% were shown in Table 4. The drug release for the formulation F4, F5 and F6 using different method of preparations with sodium starch glycolat, at the end of 15 minute the drug release was found to be 90%, 91% and 97% were shown in Table 4 and comparative dissolution study of F1 to F9 were shown in Figure 1. The formulations F7, F8 and F9 using crospovidone by different methods of preparation, the drug release was found to be 95%, 96% and 98% at the end of 15 minutes. It was concluded F9 formulation using crospovidone by melt method gives maximum drug release within 10 minutes were shown in Table 4 from the three different super disintegrating agent crospovidone with melt method formulation F9 show good drug release.

Table 4 *In Vitro* Drug Release Studies of Ondansetron HCl Mouth Dissolving Tablets

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	51.84	52.30	56.35	52.74	63.44	60.54	60.24	58.44	50.62
5	59.72	75.52	68.25	60.34	72.68	72.34	73.14	72.53	53.54
7	76.60	87.83	79.30	75.93	82.40	87.60	84.83	85.86	70.63
10	87.83	91.42	85.90	89.10	90.36	90.60	91.64	93.36	94.90
15	95.90	96.15	95.48	90.38	91.22	96.86	95.34	96.34	98.10

The IR spectrum shows that all the characteristic peaks of ondansetron HCl pure drug and formulation F9, confirming that no interaction of drug occurred with the components of the formulation was shown in Figure 1 to 4. XRD patterns of pure drug, excipients and some selected samples prepared by solvent method of solid dispersion were shown in Figure 5 to 7. DSC thermograms of pure drug, excipients and some selected samples prepared by solvent method of Solid dispersion were shown in Figure 8 to 11.

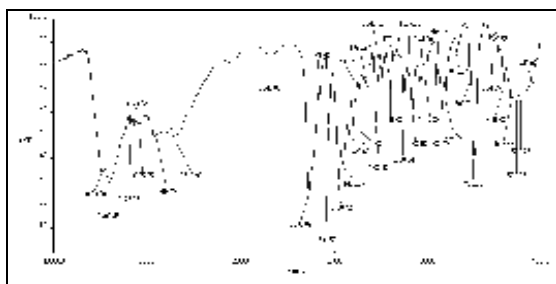


Fig 1 FTIR Spectra of Ondansetron HCl

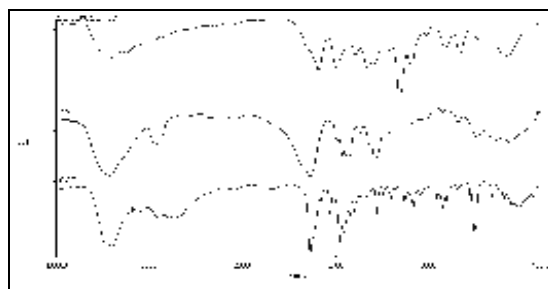


Fig 2 FTIR Spectra of Pure OSH, CP & OSH-CP

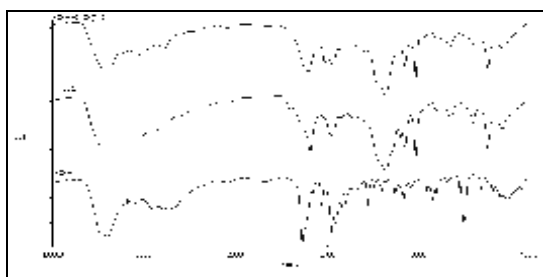


Fig 3 FTIR Spectra of Pure OSH, CCS & OSH-CCS

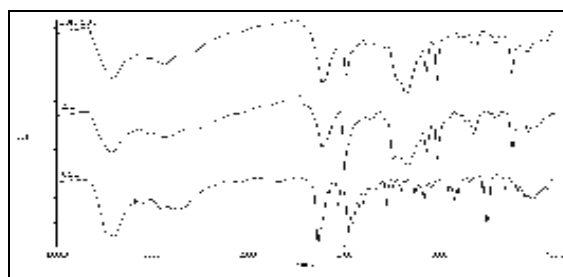


Fig 4 FTIR Spectra of Pure OSH, SSG & OSH-SSG

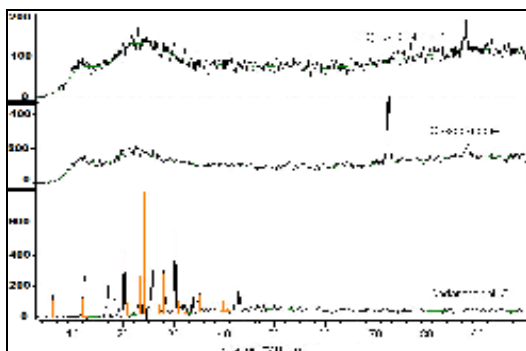


Fig 5 XRD of Pure OSH, CP & OSH-CP

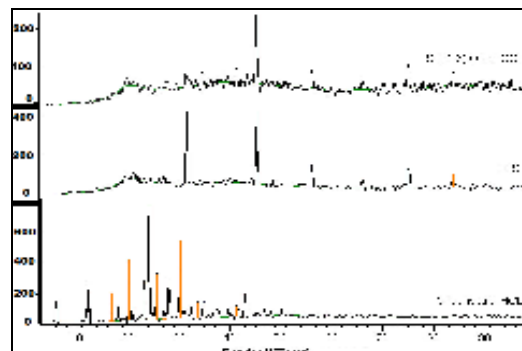


Fig 6 XRD of Pure OSH, CCS & OSH-CCS

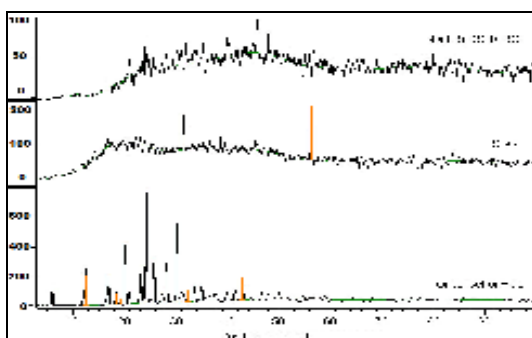


Fig 7 XRD of Pure OSH, SSG & OSH-SSG

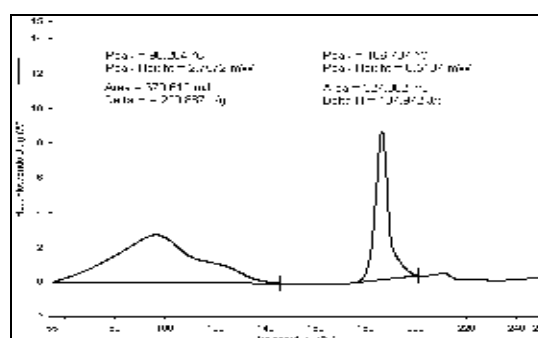


Fig 8 DSC Thermogram of OSH

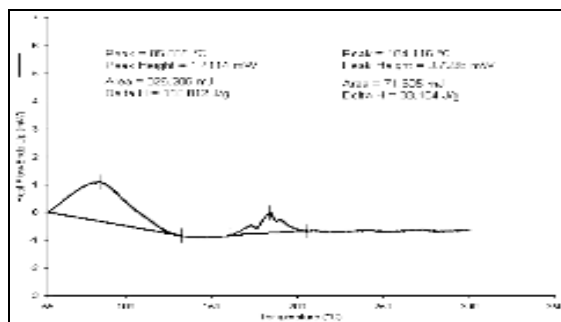


Figure 9 DSC Thermogram of OSH-CP

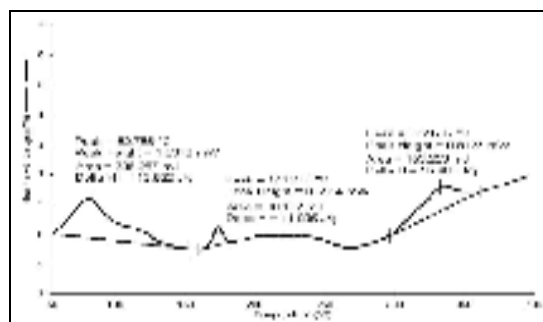


Fig 10 DSC Thermogram of OSH-CCS

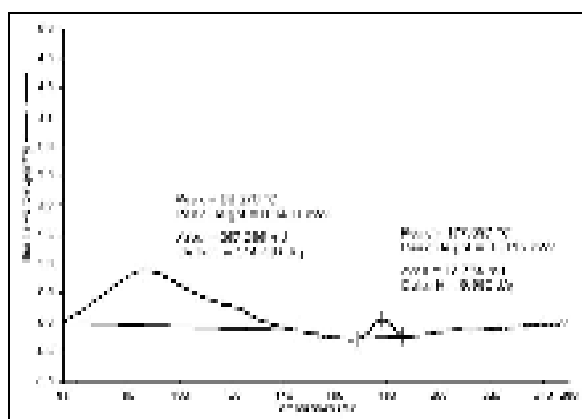


Fig 12 DSC Thermogram of OSH-SSG

Short term stability studies of the above formulations indicated that there were no significant changes in drug content and *in vitro* dispersion time at the end of 3 month period ($p < 0.05$).

Conclusion

The mouth dissolving tablets of ondansetron HCl were prepared by direct compression method using three super disintegrants, viz., croscarmellose sodium, sodium starch glycolate and crospovidone at different concentrations with microcrystalline cellulose were used along with the help of different preparations like physical mixtures and solid dispersions (solvent evaporation and melt method). A total of nine formulations were designed (F1 to F9). Among these formulations tablets containing super disintegrating agent crospovidone with solid dispersions (melt method) formulation F9 were optimized due to its fast *in vitro* dispersion when compare to other formulations and 95% drug release with in 10 min.

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