Formulation and Evaluation of Fast Dissolving Tablets of Ondansetron by Solid Dispersion in Superdisintegrants

Rajnikant M. Suthar[1], Narendra P. Chotai*[1] and Digesh D. Shah[2]

[1]A. R. College of Pharmacy and G. H. Patel Institute of Pharmacy, PO Box No.19 Motabazar, Vallabh Vidyanagar-388120, Anand, Gujarat, India.
[2]Sanofi Aventis Pharmaceuticals Ltd. Ankleshwar, Gujarat, India.

ABSTRACT

Ondansetron Hydrochloride (OSH) is a sparingly water-soluble drug. The aim of the present investigation was to prepare solid dispersion (SD) of OSH using superdisintegrants as carrier and formulate it as fast dissolving tablets (FDTs) with an objective to improve solubility and enhance dissolution of drug. SD of drug using superdisintegrants like croscarmellose sodium (CCS), crospovidone (CP), sodium starch glycolate (SSG), and low substituted hydroxy propyl cellulose (L-HPC) respectively as carriers was prepared by solvent evaporation method. The prepared SD formulations were characterized by equilibrium solubility, fourier transform infrared spectroscopy (FTIR), X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and dissolution study. FTIR spectra revealed no chemical interaction between the drug and superdisintegrants. XRPD and DSC data indicated that OSH was in the amorphous form, which explains the better dissolution rate of the drug from its solid dispersions. Various batches of FDTs (F1-F10) were prepared using selected SD formulation of drug and carrier (1:3 ratio) and evaluated for various physical parameters and drug release study. The batch containing SD formulation in CP (F3) showed fastest disintegration (3.22s), least wetting time (10.5s) and higher dissolution (97.98% drug release in 30 min). In conclusion, FDTs of OSH prepared using SD with CP seems to be promising formulations.

Keywords: OSH, Superdisintegrants, Solid dispersions, Fast dissolving tablets.

INTRODUCTION

OSH is an effective and well-tolerated antiemetic, which is used for the prevention of both chemotherapy and radiotherapy-induced emesis and nausea. It is sparingly soluble in water and well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism.[1] Mean bioavailability in healthy subjects, following oral administration of a single 8-mg tablet, is approximately 56%.

In case of poorly water soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. Various techniques, such as self emulsifying drug delivery system[2], solid dispersions[3], crystal engineering[4], complexation[5], freeze drying[6], orodispersible tablet[7], reduction of particle size, supercritical fluid methods[8], solid dispersion granules using hot melt granulation technique[9] were reported previously.

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, dysphagia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and in case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance.[10]

To overcome these drawbacks, FDTs has emerged as an alternative oral dosage forms. The basic approach used in development

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Address for correspondence
Narendra Chotai
A. R. College of Pharmacy and G. H. Patel Institute of Pharmacy, PO Box No.19 Motabazar, Vallabh Vidyanagar-388120, Anand, Gujarat, India.
E-Mail: pharmacist_chotai2002@yahoo.co.in

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of FDTs is the use of superdisintegrants which provide instantaneous disintegration of tablet after placing on tongue, thereby releasing the drug in saliva.[11–13]

A "Superdisintegrants" is an excipient, which is added to tablet to aid in the breakup of the compacted mass, when put into a fluid environment. This is especially important for immediate release product where rapid release of the product is required. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. The use of superdisintegrants is the basic approach in the development of fast disintegrating tablets (FDTs). Superdisintegrants plays a major role in the dissolution and disintegration of the tablets.[14]

Another approach used in developing such tablets is maximizing pore structure of the tablets by incorporating subliming agent. Sublimation technique was adopted after addition of a subliming agent like camphor to increase porosity of the tablets. It is likely that a porous hydrophilic matrix may easily pick up the disintegrating medium and break quickly. Therefore, it was decided to adopt the direct compression and sublimation techniques in the present investigation.[15,16]

The aim of the present study was to prepare SD of OSH using superdisintegrants (CCS, CP, SSG, and L-HPC) as carrier by solvent evaporation method with an objective to improve solubility and enhance dissolution of drug. Water dispersible superdisintegrants, a new class of tablet excipients were evaluated as carriers for enhancing the dissolution rate and bioavailability of drug was reported.[17–19]

In order to characterize the prepared dispersions, solubility study, FTIR, DSC, XRPD, as well as dissolution study were performed. FDTs were formulated from SD by direct compression and sublimation method using selected SD formulations and evaluated for various physical parameters and *in vitro* drug release study.

The mechanisms by which drug dissolution enhancement occurs by superdisinegrants are numerous and not yet well understood; however, factors such as improved wettability, increased effective surface area, loss of drug crystallinity, and solubilization effects associated with the carrier are probably responsible for their effect.[20]

MATERIALS AND METHODS

Materials

OSH, mannitol, aspartame, CCS, CP, SSG, and L-HPC were received from Zydus Cadila Ltd., Ahmedabad. Microcrystalline cellulose PH-101 was received from Relax Pharmaceuticals Ltd., Baroda. Camphor, magnesium stearate and talc were supplied from Molychem Ltd., Samir Tech Chem Pvt. Ltd., and Allied Chemical Corporation Ltd., Baroda respectively. Other reagents and chemicals used were of analytical reagent grade.

Preparation of solid dispersion and physical mixture

SD of OSH:superdisintegrants (CP, L-HPC, CCS, and SSG) were prepared by solvent evaporation method in the ratio of 1:1, 1:2, and 1:3. OSH and carrier (CP, L-HPC, CCS and SSG) were weighed accurately and triturated in a mortar and pestle for 5 min. The physical mixture was then dissolved in alcohol with constant stirring. The solvent was evaporated at 60°C for 4 h in vaccum oven (Cintex Industries, India). The co-precipitate obtained was powdered in a mortar and passed through a 80 mesh sieve and stored in a desiccator at room temperature for 24 h. Physical mixtures (PM) were also prepared in the ratio of 1:1, 1:2, and 1:3 of OSH:Carrier and mixed well in a mortar and sifted through 80 mesh.[20]

Characterization of solid dispersion

Equilibrium solubility studies[21]

The equilibrium solubility of pure OSH powder, prepared SD and PM was determined. The known excess amount (approximately 10 mg) of OSH and SD and PM (eqiuvalent to 10 mg of OSH) was placed in a sealed glass container containing 20 mL of distilled water. Samples were stirred at 37 ± 0.5ºC on a magnetic stirrer for 48 h. After attainment of equilibrium, the samples were then filtered through a 0.45 micron filter. The filtrate was diluted and assayed spectrophotometrically (UV-1601, Shimadzu Corporation, Japan) for OSH content at 310 nm. All solubility measurements were performed in triplicate.

Fourier transform infrared spectroscopy

FTIR spectra of the pure drug, excipients and prepared SD 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 powder diffraction

XRPD patterns of pure drug, superdisintegrants and prepared SD were taken using a powder diffractometer (X'pert, MP. Philips) with CuKα radiation. Powedered samples were studied by placing a thin layer of powder in conventional cavity mounts.

Differential scanning calorimetry

The DSC thermograms of pure drug, superdisintegrants and solid dispersions were recorded on a DSC (Perkin elmer Instruments, Pyris-1 DSC, USA). The samples were

weighed and heated in hermetically sealed aluminium pans over a temperature range of 50ºC to 300ºC. The system was purged with nitrogen gas at a flow rate of 80 ml/min.

Dissolution studies

The quantity of SD powder equivalent to 8 mg OSH was used for dissolution studies. Dissolution was performed in triplicate using the USP type II apparatus (Scientific USP Standards DA-60) in distilled water at 37 ± 0.5°C at 50 rpm and study was conducted for 30 min. 5 mL sample was collected at 5, 10, 15 and 30 min time intervals and volume of dissolution fluid was adjusted to 500 mL, by replacing each 5 mL aliquot withdrawn with 5 mL of distilled water. Samples withdrawn were filtered through whatmann filter paper (0.45 micron), suitably diluted and assayed for OSH by measuring absorbance at 310 nm using UV-Visible double beam spectrophotometer.[22]

Preparation of fast dissolving tablets

Ten batches of FDTs were prepared by direct compression (6 batches) and sublimation technique (4 batches) as per composition shown in Table 1. Mannitol, microcrystalline cellulose PH101, camphor (in case of sublimation technique) and aspartame were passed through 60 mesh before use. The drug as such, 1:3 SD or in 1:3 PM with CP and excipeints were blended together by tumbling for 10 min. The blend was lubricated with 1% magnesium stearate and 2% talc. The resulting blend was directly compressed in to tablets using a rotary tablet machine. (RSB-4 mini press, Rimek, India). Compressed tablets containing camphor were subjected to the process of sublimation in vaccum oven at 60ºC for 6 h.

Evaluation of tablets[23]

The Weight variation

Twenty tablets were weighed individually and the average weight was determined. The percentage deviation was calculated and evaluated for weight variation.

Thickness

The thickness of five tablets was measured using a Vernier caliper.

Hardness

Tablet hardness (tablet crushing strength), the force required for breaking a tablet in a diametric compression of five tablets was measured using monsanto hardness tester (Dolphin, Mumbai).

Friability

Pre-weighed sample of ten tablets was placed in the Roche friabilator (Erection and Instrumentation Engineers, Ahmedabad) and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The percentage friability is calculated.

In vitro *disintegration time*

The disintegration time of five tablets was measured using modified disintegration method. For this purpose, a petridish (10 cm diameter) was filled with 10 mL distilled water. The tablet was carefully put in the center of the petridish and the time for the tablet to disintegrate completely in to fine particles was noted as disintegration time.[24]

Wetting time

The wetting time of five tablets was measured by placing 5 circular tissue papers to simulate the tongue conditions in a petridish with a 10 cm diameter. 10 mL of water containing methylene blue, a water-soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.[25]

Drug content

Five tablets were crushed in mortar and powder equivalent to 8 mg OSH was dissolved in sufficient quantity of distilled water and make up volume in 100 mL volumetric

Table 1: Composition of Fast Dissolving Tablets Prepared by Direct Compression and Sublimation Method

Ingredient	F1^	F2	F3	F4	F5	F6	F7	F8	F9	F10*
	OSH	(OSH + CP)		(OSH + L-HPC)		(OSH + CCS)		(OSH + SSG)		(OSH + CP)
OSH	8 mg	–	–	–	–	–	–	–	–	
1:3 OSH-superdisintegrant SD	–	32 mg	32 mg	32 mg	32 mg	32 mg	32 mg	32 mg	32 mg	32 mg
Microcrystalline Cellulose PH-101	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg
Mannitol	100 mg	76 mg	76 mg	76 mg	76 mg	76 mg	76 mg	76 mg	76 mg	76 mg
Aspartame	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg
Magnesium Stearate	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg	1.5 mg
Talc	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg
Camphor	–	–	20 mg	–	20 mg	–	20 mg	–	20 mg	–

*F10 batch contains 1:3 PM of OSH: CP; ^F1 batch does not contain SD formulation.

flask. The solution was filtered through whatmann filter paper (0.45 micron), suitably diluted with distilled water, and analyzed at 310 nm, using a UV-Visible double beam spectrophotometer. Each sample was analyzed in triplicate.

In vitro *dissolution study of fast dissolving tablets*

USP type II apparatus was used for dissolution of FDTs. Three tablets from each batch were used to determine the dissolution of drug. The dissolution media was 500 mL distilled water, maintained at 37 ± 0.5°C to permit the sink condition.[26] The rotation speed is 50 rpm. Aliquots were withdrawn at 5, 10, 15 and 30 min time intervals and replenished immediately with same volume of fresh dissolution media. Aliquots were analyzed spectrophotometrically at 310 nm, using UV-Visible double beam spectrophotometer. The release profile of promising batches which showed higher drug release was compared with marketed product of mouth dissolving tablets of OSH.

RESULTS AND DISCUSSION

Solubility measurement

The equilibrium solubility data are shown in Table 2. The solubility of OSH powder in distilled water at 37 ± 0.5°C was 0.724 mg/ml whereas solubility of SD and PM in the range of 3.112–7.124 mg/ml and 1.960–4.316 mg/ml respectively. These findings suggest that SD had much more enhanced equilibrium solubility (5–10 folds) as compared to pure drug powder and physical mixtures (2–6 folds). The solubility of drug was increased by increasing the proportion of superdisintegrants from 1:1 to 1:3 in SD and PM. Therefore 1:3 SD formulations were selected for preparation of FDTs. It may be noted that the equilibrium solubility of SD was increased which may be probably due to decrease in crystallinity or conversion from crystalline to amorphous form.[27]

Table 2: Equilibrium Solubility Data of Different Formulations of Drug Tested in Distilled Water at 37 ± 0.5°C

Drug to Carrier ratio	Solubility (mg/ml) †		
	Drug with or without carrier	Type of formulation	
		SD	PM
1:0	OSH	0.724 ± 0.529	
1:1	OSH + CP	4.012 ± 0.812	2.826 ± 0.314
	OSH + L-HPC	3.912 ± 0.556	2.584 ± 0.286
	OSH + CCG	3.112 ± 0.534	1.960 ± 0.413
	OSH + SSG	3.564 ± 0.242	2.126 ± 0.297
1:2	OSH + CP	5.843 ± 0.926	3.424 ± 0.527
	OSH + L-HPC	5.214 ± 0.801	3.362 ± 0.713
	OSH + CCG	4.384 ± 0.612	2.728 ± 0.628
	OSH + SSG	4.957 ± 0.756	3.287 ± 0.345
1:3	OSH + CP	7.127 ± 0.768	4.316 ± 0.387
	OSH + L-HPC	6.646 ± 0.996	4.125 ± 0.811
	OSH + CCG	5.815 ± 0.769	3.816 ± 0.765
	OSH + SSG	6.185 ± 0.212	4.016 ± 0.714

SD, solid dispersion; PM, physical mixture.
†Mean ± SD; standard deviation n=3.

Fourier transform infrared spectroscopy

The I.R. spectroscopy of OSH powder, superdisintegrants and some selected samples of SD (1:3) was carried out in order to get evidence on the possible interaction of the drug with the superdisintegrants and solid state characterization of SD (Fig. 1). Pure OSH displays a peak characteristic of the N-H bending vibration at 1638.1 cm^{-1} and a band with main strong peak at 1280.62 cm^{-1} and 760.1 cm^{-1} indicative of C-N stretching and ortho-substitution phenyl C-H bending resprectively. It is evident that peaks of different functional groups of OSH in various solid dispersions were not much deviated from peaks of pure drug. In other words IR spectra of SD were identical to those of the corresponding pure drug and superdisintegrants. Consequently, the FTIR SD seemed to be only a combination of drug and superdisintegrant spectra. This result suggested that there was no interaction between drug and excipient in their combinations.

X-ray powder diffraction

The diffraction pattern of pure OSH, superdisintegrants and selected SD (1:3) is shown in Figure 2. The powder diffraction patterns of pure OSH exhibited characteristic high-intensity diffraction peaks. The powdered superdisintegrant was amorphous where it had only few peaks with very weak intensities. The crystalline structure of OSH was destroyed in SD which was evident from decrease in number and intensity of peaks. In other words these findings suggest that the OSH crystals might have converted to amorphous form in SD which was considered to be mainly responsible for the dissolution enhancement.

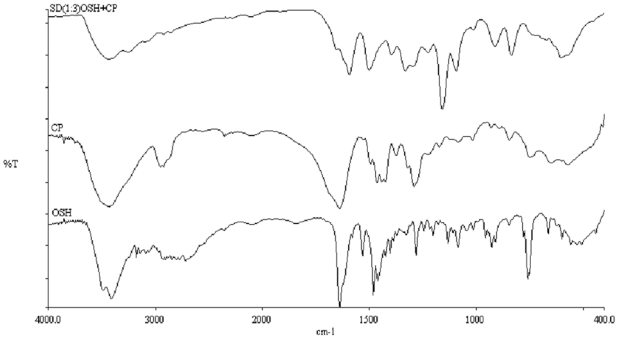

Figure 1: FTIR spectra of pure OSH, CP and 1:3 SD OSH:CP.

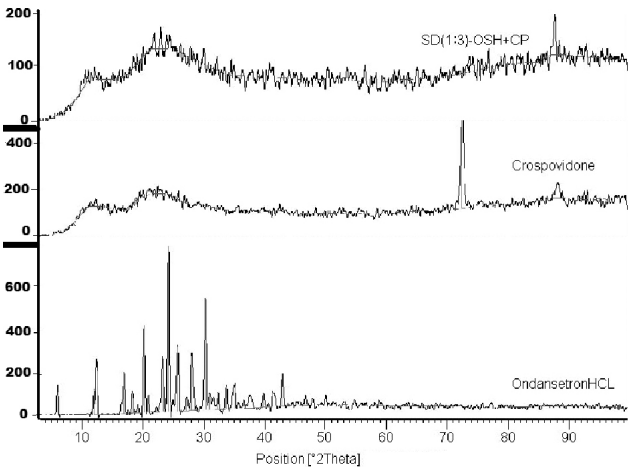

Figure 2: XRD patterns of pure OSH, CP and 1:3 SD of OSH:CP.

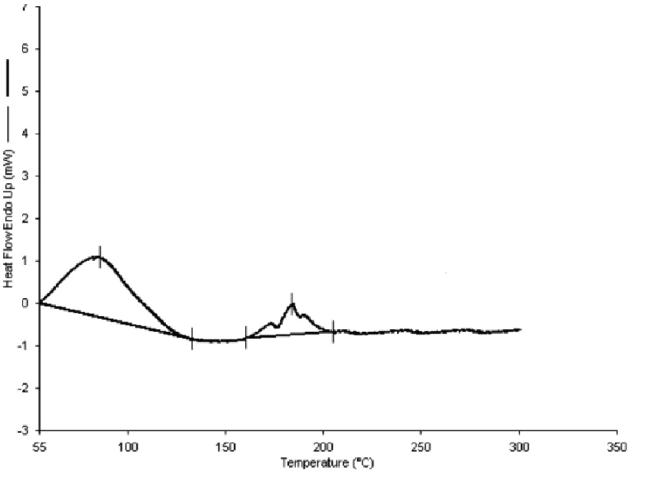

Figure 3: DSC thermogram of 1:3 SD of OSH: CP.

Differential scanning calorimetry

The DSC thermogram of OSH exhibited an endothermal peak at 186.707°C corresponding to its melting point. SD of OSH in various superdisintegrants also gave a melting peak but at slightly lower temperature in the range of 174–185°C (Fig. 3) with decrease in intensity of peak as compared to pure OSH which indicate the weak endothermic reaction between OSH and superdisintegrants. The decrease in intensity and broadening of peak indicate amorphous nature of drug which ultimately leads to dissolution enhancement.

Dissolution study

The results of dissolution studies of pure drug, different SD and PM are shown in Table 3. It can be seen from the results that the percentage drug release from SD was 98% compared to only 30% for the pure drug and 74% for PM. It is evident from the results that solid dispersions exhibited about 3.5 fold increased dissolution compared to that of pure drug. The dissolution rate was increased by increasing the proportion of superdisintegrants from 1:1 to 1:3. The order for the superdisintegrants to enhance the dissolution rate could be

Table 3: Cumulative Percentage OSH Released from Solid Dispersions and Physical Mixtures

Formulation	Ratio	Time^(min)			
		5	10	15	30
Drug (OSH)	1:0	17.96 ± 0.79	21.20 ± 0.109	23.80 ± 0.183	31.25 ± 0.424
SD (OSH + CP)	1:1	74.07 ± 0.202	77.23 ± 0.112	80.89 ± 0.134	85.51 ± 0.097
	1:2	78.30 ± 0.115	83.34 ± 0.042	85.58 ± 0.166	91.31 ± 0.053
	1:3	82.23 ± 0.203	86.44 ± 0.046	90.37 ± 0.203	97.11 ± 0.126
SD(OSH + L-HPC)	1:1	68.60 ± 0.253	71.86 ± 0.07	74.32 ± 0.141	79.34 ± 0.139
	1:2	71.03 ± 0.111	74.53 ± 0.038	77.65 ± 0.111	84.54 ± 1.136
	1:3	80.75 ± 0.095	82.34 ± 0.056	84.45 ± 0.124	90.91 ± 0.175
SD (OSH + CCS)	1:1	60.71 ± 0.097	63.74 ± 0.211	67.05 ± 0.428	72.50 ± 0.093
	1:2	64.87 ± 0.094	68.60 ± 0.078	70.19 ± 0.083	75.01 ± 0.036
	1:3	72.40 ± 0.097	75.46 ± 0.079	78.57 ± 0.084	84.43 ± 0.131
SD (OSH + SSG)	1:1	63.60 ± 0.245	66.78 ± 0.078	69.56 ± 0.134	75.33 ± 0.114
	1:2	67.03 ± 0.056	70.45 ± 0.045	74.56 ± 0.134	80.45 ± 0.067
	1:3	78.67 ± 0.086	80.98 ± 0.143	82.56 ± 0.098	87.43 ± 0.026
PM (OSH + CP)	1:3	40.92 ± 0.204	42.09 ± 0.140	45.51 ± 0.180	52.12 ± 0.145
PM (OSH + L-HPC)		38.22 ± 0.102	41.50 ± 0.139	46.33 ± 0.090	50.05 ± 0.170
PM (OSH + CCS)		34.40 ± 0.155	40.20 ± 0.146	43.50 ± 0.040	46.69 ± 0.098
PM (OSH + SSG)		37.13 ± 0.247	42.00 ± 0.132	44.41 ± 0.221	49.13 ± 0.167

OSH, OSH; PM, physical mixture; SD, solid dispersion.
^Mean ± SD; standard deviation n=3.

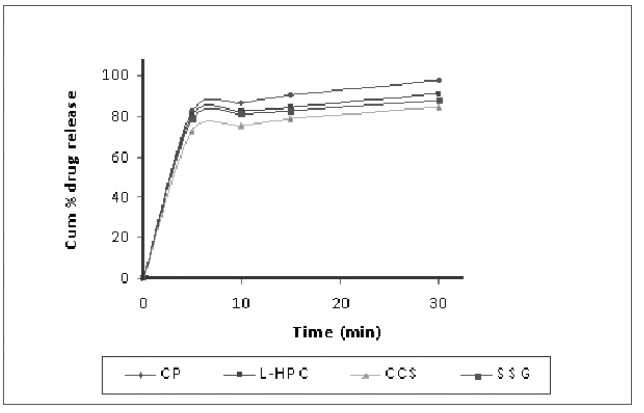

Figure 4: Comparative release profiles of pure OSH and SD formulations in a 1:3 ratio.

ranked as CP > L-HPC > SSG > CCS (Fig. 4). The mechanisms by which drug dissolution enhancement occurs from solid dispersions are numerous and not yet well understood; however, factors such as improved wettability, increased effective surface area, loss of drug crystallinity, and solubilization effects associated with the carrier are probably responsible for their effect.[20]

Evaluation of fast dissolving tablets

Tablets were prepared using direct compression and sublimation technique. Since the powder blends were free flowing, tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variations as per pharmacopoeial specifications. The thickness of all batches was found in the range of 2.7–3.0 mm which indicates that tablet prepared were of uniform thickness (Table 4).The hardness of tablets was found between 2.5 to 4.3 Kg/cm^2. Friability of the tablets was found below 1% (Table 4) indicating good mechanical resistance of tablets. The drug content was found in the range of 95.14–98.52% (Table 4).

The disintegration time of all the formulations was found in the range of 3.22–8.79s (Table 4) which was within official requirements that are less than 30 s. Wetting time was used as a parameter to correlate with disintegration time in oral cavity. This is an important criterion for understanding the capacity of disintegrants to swell in presence of little amount of water. Since the dissolution process of a tablet depends upon the wetting followed by disintegration of the tablet, the measurement of wetting time may be used as another confirmative test for evaluation of fast dissolving tablets. The wetting time of formulated tablets was found to be in the range of 10.5–22.59s (Table 4).

Dissolution results shows that more than 85% drug released after 30 min (Table 4) from all SD batches (F2–F9) as compared to batch F1 without SD (49% release) and batch F10 containing PM (75% release). It can be inferred from the results that batch containing CP (F2 and F3) exhibited higher dissolution rate (97% release after 30 min) as compared to that of batch containing CCS, L-HPC, and SSG (F4–F9). F3 batch was selected as promising formulation because of higher drug release, fastest disintegration time (3.22 s) and least wetting time (10.5 s).

Comparison of release profile with marketed product

The results revealed that promising batch exhibited comparable release profile with marketed mouth dissolving tablet (MMDT) as shown in Figure 5.

Table 4: Results of Evaluation Parameters of Fast Dissolving Tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Average weight of tablet (mg) (n=20)	152.05 (1.069)	149.77 (2.362)	150.84 (1.676)	148.18 (2.003)	151.18 (1.783)	149.92 (1.039)	152.45 (1.112)	145.56 (2.897)	151.67 (2.675)	153.75 (2.456)
Thickness (mm) (n=5)	3 (0.110)	2.9 (0.055)	2.8 (0.114)	2.8 (0.122)	2.9 (0.217)	2.9 (0.045)	2.8 (0.084)	2.7 (0.164)	2.7 (0.259)	3.0 (0.110)
Hardness (Kg/cm^2) (n=5)	3.0 (0.134)	4.3 (0.023)	4.3 (0.037)	3.5 (0.103)	2.8 (0.094)	3.3 (0.114)	3.0 (0.045)	3.2 (0.065)	2.5 (0.051)	4.1 (0.141)
Friability (%) (n=3)	0.421 (0.0052)	0.160 (0.0029)	0.189 (0.0023)	0.279 (0.0074)	1.003 (0.0053)	0.206 (0.0022)	0.457 (0.0046)	0.680 (0.0058)	2.313 (0.0085)	0.196 (0.0012)
Disintegration time (sec) (n=5)	7.56 (0.428)	3.64 (0.249)	3.22 (0.161)	5.73 (0.317)	4.99 (0.175)	8.79 (0.479)	6.68 (0.306)	4.19 (0.316)	3.84 (0.114)	4.23 (1.403)
Wetting time (sec) (n=5)	14.12 (1.473)	12.68 (0.675)	10.50 (1.347)	17.12 (0.812)	14.49 (0.504)	32.80 (0.933)	22.59 (1.241)	16.29 (0.541)	11.45 (0.845)	13.22 (1.364)
% Drug content (n=10)	98.21 (1.551)	97.94 (1.262)	97.13 (1.126)	95.97 (0.970)	95.31 (1.511)	96.66 (1.173)	96.38 (1.683)	97.02 (1.626)	95.14 (1.311)	98.52 (0.935)
% Drug release after 30 min (n=3)	49.47 (0.713)	97.78 (0.564)	98.15 (1.383)	92.66 (1.614)	91.45 (0.911)	85.65 (0.683)	86.62 (0.845)	90.29 (2.031)	91.81 (1.729)	74.94 (0.924)

Value in the parenthesis indicates standard deviation.

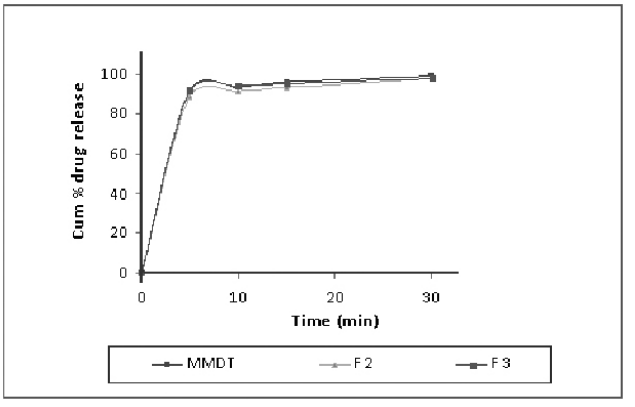

Figure 5: Comparative *in vitro* release profile of promising batch and marketed product.

CONCLUSION

In conclusion, fast dissolving tablets of Ondansetron prepared using solid dispersion with crospovidone seems to be promising formulations and further *in vivo* study may be carried out.

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