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In Vitro Dissolution Enhancement of Ondansetron by Solid Dispersion in Superdisintegrants

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ABSTRACT

Ondansetron hydrochloride (OSH) is a highly selective and potent antagonist of 5-hydroxytryptamine at $5HT_3$ receptors in the gastrointestinal tract where it blocks both sites of serotonin induced nausea and vomiting. Physical mixtures and solid dispersions of the drug using superdisintegrants as carriers were prepared by a solvent method at different drug–carrier (w/w) ratios and evaluated with an objective of enhancing the dissolution rate of OSH from solid dispersion. Equilibrium solubility studies were performed for drug–carrier interactions in solution, and Fourier transform infrared (FTIR) spectroscopy, X-ray powder diffraction (XRD), and differential scanning calorimetry (DSC) studies were carried out to characterize the solid dispersions. FTIR spectra reveal no chemical interaction between the drug and superdisintegrants. XRD and DSC data indicate OSH was in the amorphous form, which explains the better dissolution rate of the drug from its solid dispersions. A marked enhancement in the dissolution of OSH was observed with all the superdisintegrants.

KEYWORDS: Ondansetron hydrochloride (OSH), superdisintegrants, solid dispersions, dissolution.

INTRODUCTION

Ondansetron hydrochloride (OSH) is an effective and well-tolerated antiemetic that is used for the prevention of both chemotherapy- and radiotherapy-induced emesis and nausea. OSH is sparingly soluble in water (*1*). It is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects following administration of a single 8-mg 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 the gastrointestinal tract (GIT). Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs in general include micronization, the use of surfactants, and the formation of solid dispersions (*2*).

The two basic procedures used to prepare solid dispersions are the fusion and cosolvent techniques. In the fusion method, a physical mixture of an active agent and a water–soluble carrier is heated until it is melted. The melt is solidified rapidly in an ice bath with vigorous stirring, pulverized, and then sieved. The solidification process can be achieved on stainless steel plates attached to a cooling system to favor rapid heat loss. Spray congealing from a modified spray drier onto a cold metal surface has also been used. In the cosolvent technique, drug and carrier are dissolved in a common solvent, and then the solvent is evaporated under vacuum or in an oven to produce a solid dispersion (*3*, *4*).

The aim of the present study was to formulate and evaluate the physicochemical properties of prepared solid dispersions of OSH in superdisintegrants. DSC, XRD, and FTIR as well as dissolution and solubility studies were performed to characterize the prepared dispersions.

MATERIALS

OSH, croscarmellose sodium (CCS), crospovidone (CP), sodium starch glycolate (SSG), and low-substituted hydroxypropyl cellulose (L-HPC) were received as gift samples from Zydus Cadila Ltd., Ahmedabad. Other reagents and organic solvents used were of analytical grade.

OSH is a white to off-white crystalline powder available in base and chloride salt forms. The base is sparingly soluble in water and alcohol, soluble in methanol, slightly soluble in isopropyl alcohol and dichloromethane, and very slightly soluble in acetone, chloroform, and ethyl acetate.

METHODS

Preparation of Solid Dispersions and Physical Mixtures

Solid dispersions containing drug (OSH) and excipient in the proportions of 1:1, 1:2, and 1:3 were prepared employing CP, L-HPC, CCS, and SSG as excipients. OSH was dissolved in alcohol to a clear solution. The OSH solution

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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 a vacuum oven (Sintex Industries, India), and the coprecipitate obtained was powdered in a mortar, passed through an 80-mesh sieve, and stored in a desiccator at room temperature for 24 h. For the preparation of physical mixtures, OSH and excipient (CP, L-HPC, CCS, and SSG) were passed through a 100-mesh sieve and then accurately weighed in the proportions of 1:1, 1:2, and 1:3. They were mixed well in a mortar and sifted through an 80-mesh sieve.

Characterization of Solid Dispersions

Equilibrium Solubility Studies

The equilibrium solubilities of pure OSH powder, prepared solid dispersions, and physical mixtures in distilled water were determined at 37 ± 0.5 °C. A known excess amount (approximately 10 mg) of OSH, solid dispersion, and physical mixture (equivalent to 10 mg of OSH) were placed in sealed glass containers containing 20 mL of distilled water. Samples were stirred at 37 ± 0.5 °C on a magnetic stirrer for 48 h. Each sample was then filtered through a 0.45-µm filter. The filtrate was diluted and assayed spectrophotometrically (Shimadzu UV-1601, Shimadzu Corp, Japan) for OSH content at 310 nm.

Preparation of Standard OSH Stock Solution (100 µg/mL)

A 10-mg sample of OSH standard was weighed and transferred to a 100-mL volumetric flask. Thirty milliliters of distilled water was transferred to the flask, which was then sonicated for 10 min. The flask was shaken and brought to volume with distilled water to give a solution containing 100 µg/mL OSH. All solubility measurements were performed in triplicate.

Fourier Transform Infrared Spectroscopy

FTIR spectra of the pure drug, excipients, and prepared solid dispersions were obtained on a PerkinElmer 1600 FTIR spectrometer (Spectrum GX FTIR system, PerkinElmer, USA). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400–4000 cm^{-1}, and the resolution was 1 cm^{-1}.

X-ray Diffraction

XRD patterns of pure drug, superdisintegrants, and prepared solid dispersions were obtained using a powder diffractometer (Philips X'Pert MPD system) with CuKα radiation. Samples were prepared 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 (PerkinElmer Instruments, Pyris-1 DSC). The samples were weighed and heated in hermetically sealed aluminum pans over a temperature range of 50–300 °C. The system was purged with nitrogen gas at a flow rate of 80 mL/min.

Dissolution Studies

Dissolution experiments were performed in triplicate using USP Apparatus 2 (Scientific USP Standards DA-60, Veego, India) in 0.1 N HCl to simulate gastric fluid conditions at 37 ± 0.5 °C at a speed of 50 rpm. Powdered samples of each preparation equivalent to 8 mg of OSH were added to the dissolution medium. The powder did not float on the surface. Dissolution studies were conducted for 30 min, and 5-mL samples were collected at 5-, 10-, 15-, and 30-min intervals. The volume of dissolution fluid was adjusted to 500 mL by replacing each 5-mL aliquot withdrawn with 5 mL of dissolution medium, pre-warmed at 37 ± 0.5 °C. Samples withdrawn were filtered through Whatman filter paper (0.45-µm), suitably diluted, and assayed for OSH by measuring absorbance at 310 nm using a Shimadzu UV-1601 Spectrophotometer (Shimadzu Corporation, Japan).

RESULTS AND DISCUSSION

Solubility Measurement

The equilibrium solubility data are presented in Table 1. The solubility of OSH powder in distilled water at 37 ± 0.5 °C was 0.724 mg/mL, whereas solubilities of the solid dispersion and physical mixture were in the ranges of 3.112–7.124 mg/mL and 1.960–4.316 mg/mL, respectively (Table 1). These findings suggest that solid dispersions had much more enhanced equilibrium solubility (5–10-fold) as compared with pure drug powder and physical mixtures (2–6-fold). The solubility in a physical mixture may be increased due to trituration of the drug with superdisintegrants in a mortar, thereby converting it to the amorphous form, and because of the solvent properties of superdisintegrants.

Fourier Transform Infrared Spectroscopy

IR spectroscopic studies of OSH powder, superdisintegrants, and some selected samples of solid dispersions were carried out to determine possible interactions of the drug with the superdisintegrants and to characterize the solid-state dispersions. Pure OSH displays a peak characteristic of the NH bending vibration at 1638.1 cm^{-1} and peaks at 1280.62 cm^{-1} and 760.1 cm^{-1}, which are indicative of CN stretching and ortho-substituted phenyl CH bending, respectively. Peaks of different functional groups of OSH in various solid dispersions did not deviate much from peaks of pure drug except in the OSH–CP solid dispersion. IR spectra of the solid dispersions are identical to those of the corresponding pure drug and superdisintegrants. Consequently, the FTIR spectra of solid dispersions seem to be a combination of only drug and superdisintegrant spectra.

X-ray Diffraction

The powder diffraction patterns of pure OSH exhibit characteristic high-intensity diffraction peaks. The powdered superdisintegrants were amorphous, where the XRD patterns had only few peaks with very weak intensities. The crystalline structure of OSH was destroyed in all solid dispersions,

Table 1. Equilibrium Solubility of Different Formulations of OSH Tested in Distilled Water at 37 ± 0.5 °C

Drug–Carrier Ratio	Solubility (mg/mL)[a]		
	Drug (with or without carrier)	Formulation Type[b]	
		SD	PM
1:00	OSH	0.724 ± 0.523	
1:01	OSH + CP	4.012 ± 0.812	2.826 ± 0.314
	OSH + L-HPC	3.912 ± 0.556	2.584 ± 0.286
	OSH + CCS	3.112 ± 0.534	1.960 ± 0.413
	OSH + SSG	3.564 ± 0.242	2.126 ± 0.297
1:02	OSH + CP	5.843 ± 0.926	3.424 ± 0.527
	OSH + L-HPC	5.214 ± 0.801	3.362 ± 0.713
	OSH + CCS	4.384 ± 0.612	2.728 ± 0.628
	OSH + SSG	4.957 ± 0.756	3.287 ± 0.345
1:03	OSH + CP	7.124 ± 0.768	4.316 ± 0.387
	OSH + L-HPC	6.646 ± 0.996	4.123 ± 0.811
	OSH + CCS	5.815 ± 0.769	3.815 ± 0.765
	OSH + SSG	6.185 ± 0.212	4.016 ± 0.714

[a] *Mean ± SD; standard deviation (n = 3).*
[b] *PM: physical mixture; SD: solid dispersion.*

Table 2. Cumulative Percentage OSH Released from Solid Dispersions and Physical Mixtures

Formulation[a]	Ratio	Time (min)[b]			
		5	10	15	30
Pure 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

[a] *PM, physical mixture; SD, solid dispersion.*
[b] *Mean ± SD; standard deviation (n = 3).*

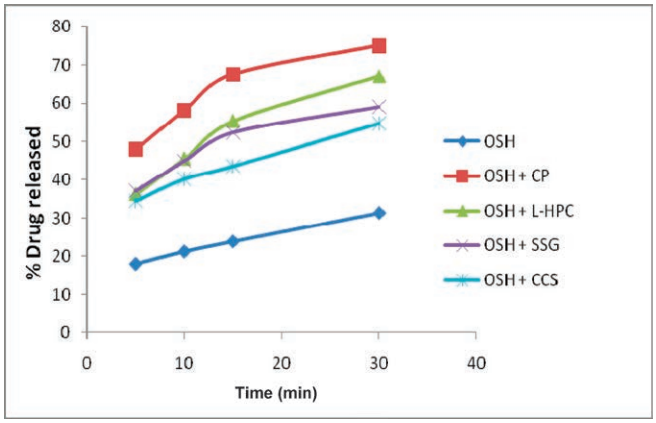

Figure 1. Comparative release profiles of pure OSH and PM formulations in a 1:3 ratio.

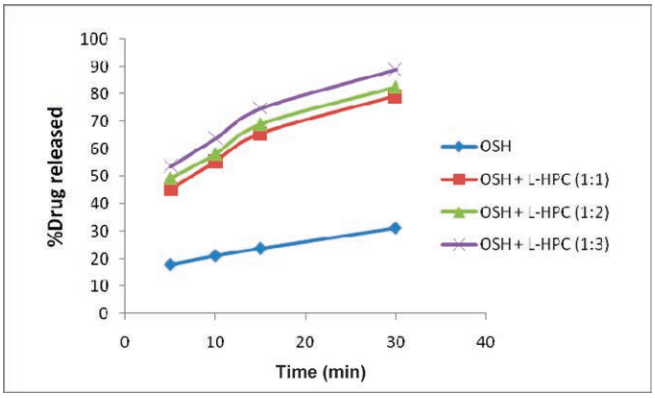

Figure 3. Cumulative percentage drug released from OSH–L-HPC solid dispersions.

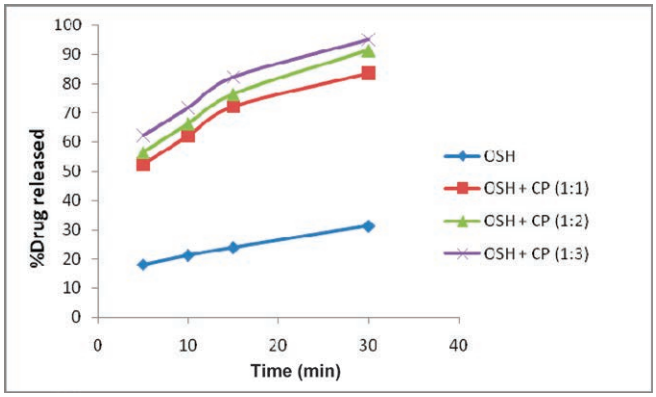

Figure 2. Cumulative percentage drug released from OSH–CP solid dispersions.

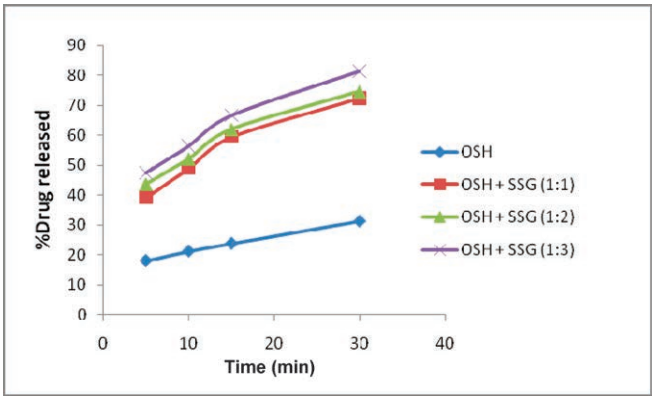

Figure 4. Cumulative percentage drug released from OSH–SSG solid dispersions.

which is evident from the decrease in the number and intensity of peaks in all solid dispersions. Thus, the crystalline structure of OSH was converted to the amorphous form in solid dispersions and physical mixtures.

Differential Scanning Calorimetry

The DSC thermogram of OSH exhibits an endothermic peak at 186.707 °C, which corresponds to its melting point. Solid dispersions of OSH in various superdisintegrants also gave melting peaks but at slightly lower temperatures in the range of 174–185 °C with a decrease in peak intensity as compared with pure OSH. This is consistent with a weak endothermic reaction between OSH and superdisintegrants. The decrease in intensity and broadening of peak of OSH was observed in all solid dispersion formulations.

Dissolution Study

The results of the dissolution studies of pure drug, solid dispersions, and physical mixtures are shown in Table 2.

The percentage of drug dissolved from solid dispersions within 30 min was 98% compared with only 30% for the pure drug and 74% for physical mixtures. Solid dispersions exhibited about a 3.5-fold increase in dissolution compared with the pure drug. The dissolution rate was increased by increasing the proportion of superdisintegrants in the physical mixtures (Figure 1) and solid dispersions from 1:1 to 1:3 (Figures 2–5). The rank order of the superdisintegrants to enhance the dissolution rate is CP > L-HPC > SSG> CCS (Table 2). The dissolution study revealed that the OSH–CP (1:3) solid dispersion system had the maximum dissolution rate (98% release within 30 min) followed by the OSH–L-HPC (1:3) system, OSH-SSG (1:3) system, and finally the OSH-CCS (1:3) system (Figure 6). The mechanisms by which superdisintegrants enhance drug dissolution are not yet well understood. However, factors such as improved wettability, increased surface area, loss of crystalline structure of drug, and solubilization effects associated with the carrier are probably responsible for their effect.

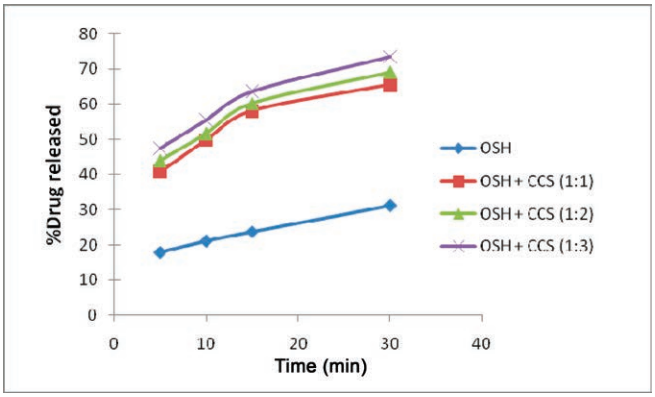

Figure 5. Cumulative percentage drug released from OSH–CCS solid dispersions.

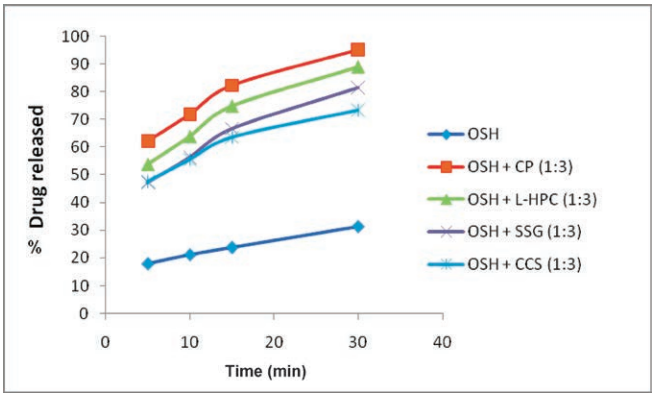

Figure 6. Comparative release profiles of pure OSH and SD formulations in a 1:3 ratio.

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