International Journal of Current Pharmaceutical Research

Vol 2, Issue 2, 2010

Research Article

PREPARATION AND CHARACTERIZATIONOF ONDANSETRON HYDROCHLORIDE MICROSPHERES USING VARIOUS CELLULOSE POLYMERS

SUNITHA S[1*], AMARESHWAR P[2], SANTHOSH KUMAR M[1]

[1]St.Marys College of Pharmacy, Secunderabad, A.P-500025, [2]Osmania University, College of Technology, A.P-500007.

E Mail: sunithasampathiphd@gmail.com

Received 22 Dec 2009, Revised and Accepted 10 Jan 2010

ABSTRACT

The present study was aimed to prepare microspheres for sustained release of ondansetron hydrochloride using various cellulose polymers such as ethyl cellulose, cellulose acetate phthalate, cellulose acetate by employing solvent evaporation technique. Microspheres were characterized for the particle size distribution, wall thickness by scanning electron microscopy (SEM), angle of repose, bulk density, percent drug content, entrapment efficiency and *in vitro* dissolution studies. Drug excepient compatibility was determined by FTIR and DTA. Accelerated stability studies were also carried out following ICH Guidelines. SEM revealed that microspheres were found spherical, free flowing and porous. The entrapment efficiency and wall thickness was found in between 69.44% & 40.35%, 117.57µ & 71.82µ respectively. The drug release was extended maximum upto 12hours with ethyl cellulose FTIR and DSC results showed ondansetron was compatible with excepients. The curve fitting data revealed that the release followed first order kinetics and higuchi's and peppa's plots stated non-fickian and diffusion controlled.

Keywords: Microspheres, ondansetron hydrochloride, Cellulose polymers, Sustained release, Stability studies.

INTRODUCTION

Ondansetron is a novel and specific antagonist of the 5-HT receptor indicated for chemotherapy- induced nausea and vomiting in cancer patients[1]. The half-life in plasma has been reported to be 4-5 hours. The shorter biological half-life and frequent dosing in chemotherapy-induced nausea and vomiting make it as an ideal candidate for sustained release drug delivery system. Therefore the objective of the work is to provide a sustained action pharmaceutical composition containing ondansetron in a modified release formulation, to maintain the blood levels of the active ingredient for a prolonged period of time. Microencapsulation is of the technique to sustain the release rate of the drug. Microencapsulation is defined as the application of a thin coating to individual core material that has an arbitrary particle size range from 5 to 5000µm[2, 3]. Microencapsulation can improve the absorption of a drug and reduce side effects such as irritation of the gastric intestinal mucosa[4]. Only limited studied on ondansetron extended release formulation has been carried out using cellulose derivatives. Rectal[5] and nasal[6] absorption of ondansetron have been reported.

MATERIALS AND METHODS

Materials

Ondansetron hydrochloride was obtained as a gift sample from Dr. Reddy's (Hyderabad). Cellulose acetate phthalate and Cellulose acetate was obtained from Nacto pharma (Hyderabad) Ethyl cellulose as a gift sample from Matrix Laboratories (Hyderabad). All the solvents are procured of Merck. All other chemicals and reagents used in the study were of analytical grade.

Methods

Preparation of microspheres

Ondansetron microspheres were prepared by the emulsion solvent evaporation method. The polymers (ethyl cellulose, cellulose acetate, and cellulose acetate phthalate)[7-9] were dissolved in acetone; by stirring the mixture at 800rpm the author dispersed the drug particles in liquid paraffin (50% heavy+50% light) containing 1% w/w polysorbate.[10-12] The polymer solution was added slowly to the drug dispersion by means of a burette. The mixture was agitated at room temp (25°c) until the acetone (polymer solvent) was evaporated.[13-15] The rate of stirring was kept constant for all the batches and for all the methods and the ratio of drug to polymer was varied as (D: P as 1:1, 1:2, 1:3) and labeled as F1 to F9. The liquid paraffin was decanted and the microspheres were collected, washed with petroleum ether to remove any remaining oil phase and dried under, reduced pressure for at least 12 hours. Table No. 1.

Table 1: Formulation table

Formulation	Drug (mg)	Ethyl Cellulose (mg)	Cellulose acetate (mg)	Cellulose acetate phthalate (mg)	Drug: Polymer
F1	300	300	-	-	1:01
F 2	300	600	-	-	1:02
F 3	300	900	-	-	1:03
F 4	300		300	-	1:01
F 5	300	-	600	-	1:02
F 6	300	-	900	-	1:03
F 7	300	-		300	1:01
F 8	300	-	0	600	1:02
F 9	300	-	-	900	1:03

CHARACTERIZATION OF MICROSPHERES

Scanning electron microscopy (SEM)

Morphological characterization of the microspheres was carried using scanning electron microscopy (SEM-LEICA, S430, U.K.). For SEM the double sided sticking tape coated with gold film (thickness 200nm) was used under the reduced pressure (0.001torr).

Particle Size analysis

All the batches prepared were analyzed for particle size. Microspheres were placed on the set of standard sieves ranging from sieve No. 16# – 60#. The sieves were arranged in such a way that in descending order of the mesh size 16# on the top and 60# mesh in the bottom. The microsphere passed through the set of sieves and the amount retained on each sieve was weighed and the average mean diameter was determined.

Assay of ondansetron hydrochloride

To determine the total drug content of the microspheres 100mg of microspheres was ground to a fine powder and dissolved in 5ml of acetone and diluted with phosphate buffer pH 7.4 to 100ml. the drug content was determined spectrophotometrically at 272nm. Three determination of the microspheres content from the same batch for each ratio and method was performed.

Encapsulation efficiency (EE)

Drug loaded microspheres were weighed and dissolved in phosphate buffer PH 7.4 and mixture was filtered. The percent entrapment was calculated using the Eq (1).

$$\text{Encapsulation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad \text{Eq (1)}$$

Wall thickness

The wall thickness of the prepared microspheres was calculated using the Eq (2).

$$h = ř\,(1\text{-}P)\,d_1/3(Pd_2 + (1\text{-}P)\,d_1 \quad \text{Eq (2)}$$

Fourier Transforms infrared Spectroscopy (FT-IR)

The FT-IR spectra acquired were taken from dried samples. An FT-IR (Thermo Nicolet 670) spectrometer was used for the analysis in the frequency range between 4000cm^{-1} and 400 cm^{-1}.

Differential Thermal Analysis (DTA)

DTA of ondansetron hydrochloride and drug loaded microspheres were performed by using Seiko (Japan) DTA. Samples were sealed in aluminium pans and the DTA thermograms were reported at a heating rate of 10°/min from 20°C to 300°C.

X ray diffractometer (XRD-shimadzu 7000)

X ray diffractometry was used for diffraction studies. XRD studies were performed on the samples by exposing them to cupper (cu kα) radiation (40kv,30mA) and scanned from 2°C t0 80°C, 2 theta(θ) at a step size of 0.045° and step time of 0.5 sec. XRD analysis was performed on the pure drug and for the prepared formulation of microspheres with various polymers.

In vitro drug release studies

In vitro dissolution studies were performed using (USP type II dissolution apparatus). The rotating basket method specified in USP-XXI at 75 rpm. The microspheres were weighed and tied in the muslin bag and placed in the basket. The dissolution medium (900ml) consisted of 0.1M hydrochloric acid for the first 2 hours and then changed to phosphate buffer pH 7.4 from the 3rd hour. The temperature was maintained at 37°C. An aliquot of (5ml) sample was withdrawn at specified time interval and replaced with an equivalent volume of dissolution fluid. Drug content was determined by UV-Visible spectrophotometer (Schimazdu UV 1700 E 23) at 245nm. The release studies were conducted in triplicate.

Determination of stability of the microspheres

The microspheres prepared in the present study were filled in the hard gelatin capsules (No.1) and stored in HDPE container at RT 37°C, and 45°C for 6 months as per ICH guidelines. The samples were then characterized for % drug content.

RESULTS

Prepared microspheres were found to be discrete, spherical and free flowing and have nearly uniform size. Fig.4, 5. SEM results revealed among the various formulations the formulation F5 showed maximum percentage yield and F7 formulation showed highest drug entrapment. The average mean diameter of the microspheres was found to be ranging between 71.82µ to 117.57µ. Table No. 2. Fig. 2. The FTIR spectra of the pure drug and microspheres with polymers were compared and the characteristic peak for microspheres in spectra was found to be super imposable to that of the pure drug. There were no extra peaks, which gave evidence that there was no drug polymer interaction. The FTIR spectrum of the physical mixture of drug and polymer showed no significant shift or reduction in intensity of peaks of ondansetron. A broad band of bonded -OH of ondansetron was observed from 3481cm^{-1} to 3245.97 cm^{-1} in pure drug also found in samples and a sharp prominent peaks found at 2926cm^{-1} because of –CH stretching indicating presence of methyl group and at 1726 cm^{-1} due to -C=O stretching indicating keto group and these peaks are found prominent and clear in sample spectra also. Fig. 6.

The X-ray diffractogram of ondansetron confirms its crystalline nature, as evidenced from the number of sharp and intense peaks. The diffractogram of ondensetron with polymers showed diffused peaks, indicating polymers amorphous nature and sharp intense peaks indicates the crystalline nature of the drug. Diffraction pattern of the drug with polymer mixture showed simply the sum of the characteristic peaks of pure drug and the diffused peaks of polymer, indicating presence of drug in the crystalline state. Diffraction pattern of sample spectra represents availability of crystalline peaks of drug situated at 12.49°, 23.25° and 24.13° (2θ) similar to pure drug with corresponding peak intensities of 2598, 3689,and 3246 linear counts respectively. This indicates crystalline nature of the drug. The peak intensities for formulation were also measured at the same 2θ scattered angles of 12.68°, 23.44° and 24.46°, and the corresponding linear counts were found to be 664, 744, 677 respectively in case of cellulose acetate phthalate, 596, 1025, 765 in case of cellulose acetate microspheres. In case of ethyl cellulose microspheres formulations there was a shift of peak with corresponding 2θ. XRD patterns of ethyl cellulose ondansetron formulations exhibits sharp peaks at 2θscattered angle 11.05°, 14.72°, 26.20° with corresponding peak intensities 800, 1543, 957 linear counts respectively. Based on the peak intensities it shows that the degree of crystallinity of drug was reduced in presences of the polymers and the decrease of crystallintiy of the drug is in the following order of CAP > CA > EC. The effect of orientation is much more in case of ethyl cellulose formulation of the drug thereby the overall intensity of the drug decreased. Fig. 8.

Table 2: % drug content, angle of repose, average mean diameter (AMD) and wall thickness

Formulation	%DC	Angle of repose	AMD µ	Wall thickness
F1	59.75	29.24	394.41	71.82
F 2	44.22	28.16	410	74.82
F 3	40.35	26.83	424.81	77.36
F 4	65.32	29.76	476.03	102.2
F 5	69.65	29.32	493	105.96
F 6	62.65	28.6	547.47	117.57
F 7	52.56	29.52	343.5	71.7
F 8	55.33	30.24	392.8	81.99
F 9	56.02	29.33	404.99	84.54

Table 3: Curve fitting data for all formulations from F1-F9

Formulation	First order Equation			Higuchi's Equation			Peppa's double Log Plot	
	Slope	Rate constant (K) mg. hr^{-1}	Regression coefficient (R^2)	Slope	Rate constant (K) mg. hr^{-1}	Regression coefficient (R^2)	Slope	Regression coefficient (R^2)
F1	0	1.989	0.938	2.413	7.615	0.915	0.559	0.932
F2	0.002	1.993	0.939	1.889	7.709	0.889	0.574	0.906
F3	0	1.984	0.966	1.409	4.093	0.905	0.449	0.892
F4	0.006	2.203	0.925	6.022	3.264	0.962	0.505	0.902
F5	0.004	2.038	0.982	5.336	1.875	0.978	0.524	0.98
F6	0.003	2.076	0.917	4.704	3.091	0.98	0.585	0.997
F7	0.003	2.153	0.764	5.162	-7.081	0.976	0.573	0.979
F8	0.004	2.24	0.876	6.069	-16.58	0.986	0.66	0.995
F9	0.004	2.103	0.901	5.685	-15.31	0.969	0.662	0.985

The DTA thermograms proved the compatibility of the drug and polymers used where no deviations were found in the graph of the drug with polymer in comparison with pure drug and the mid points of the peak was found at same temperature in between 90ºC -110ºC and 190ºC -210ºC. Fig. 7.

Maximum release of ondansetron hydrochloride from the various formulations was achieved with in 12-14 hours or longer. Fig. 3. The release mechanism of the ondansetron formulation was determined by comparing their respective correlation coefficients. Drug release from microspheres prepared by using ethyl cellulose gave good release rate retardation when compared to other polymers. From the release profiles it can be understood that the polymer used influences the release rate of the drug a lot.

DISCUSSION

The formulation followed first order release kinetics, higuchi's and peppas release plots stated non-fickian and diffusion controlled. Table No. 3. The release mainly depended on the ratio of the polymer. In ondansetron spectrum C-H, O-H, N-H bands were found. The same bands were also found in the spectra of the formulations indicating that there was no drug-polymer interaction. The accelerated stability studies showed the stable nature of the drug and showed a good correlation between the original and the aged samples. Good entrapment efficiency was observed. SEM demonstrated the spherical nature of the microspheres and the presence of the drug particles on the surface. Fig. 4, 5.

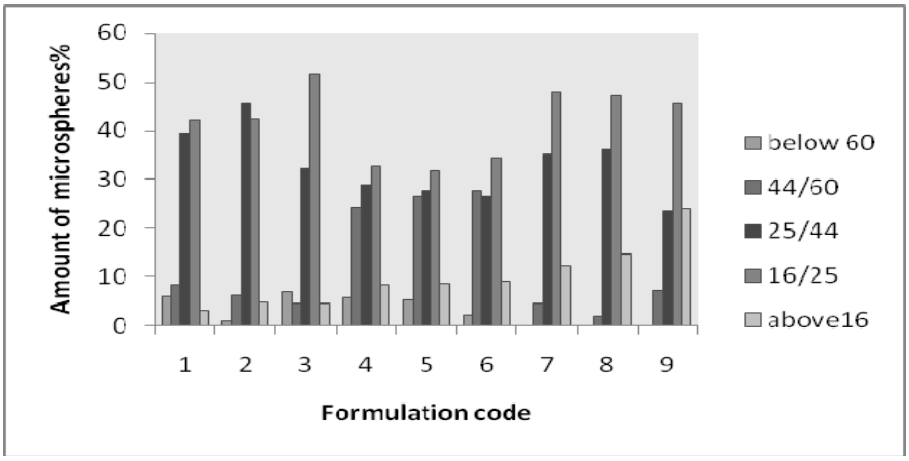


Fig. 1: Particle size distribution of prepared microsphere

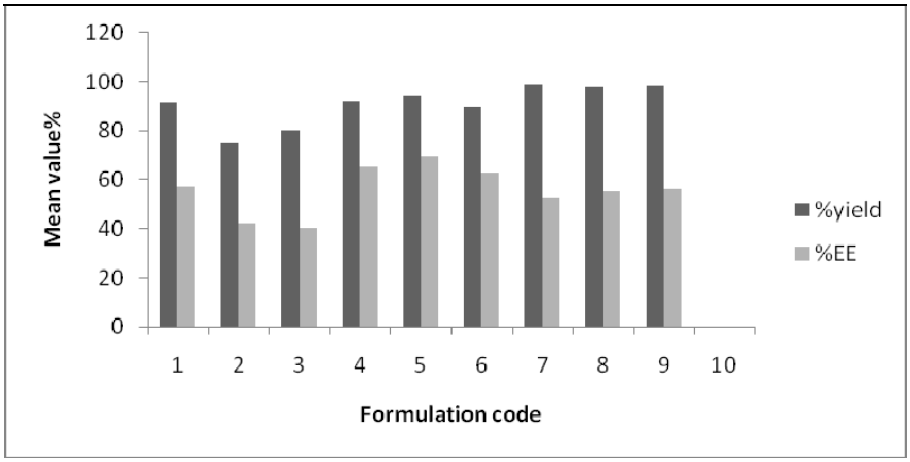


Fig. 2: % Yield and Encapsulation efficiency

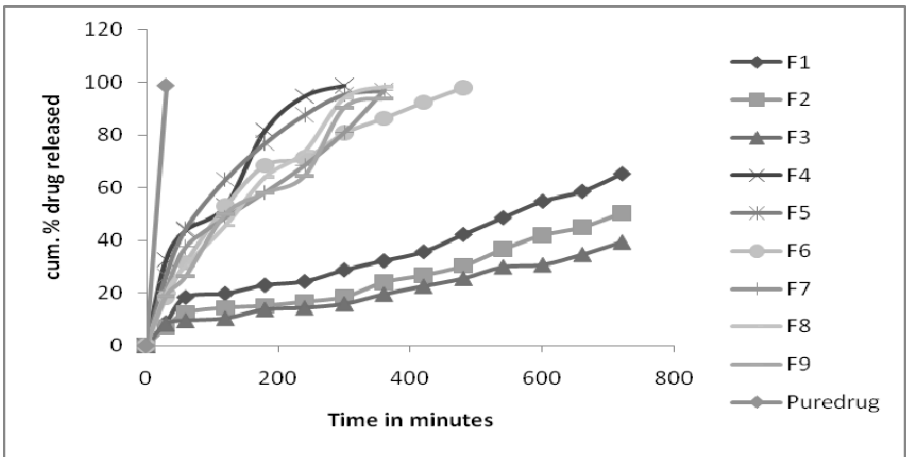


Fig. 3: Cumulative % drug release of prepared microspheres F1-F9

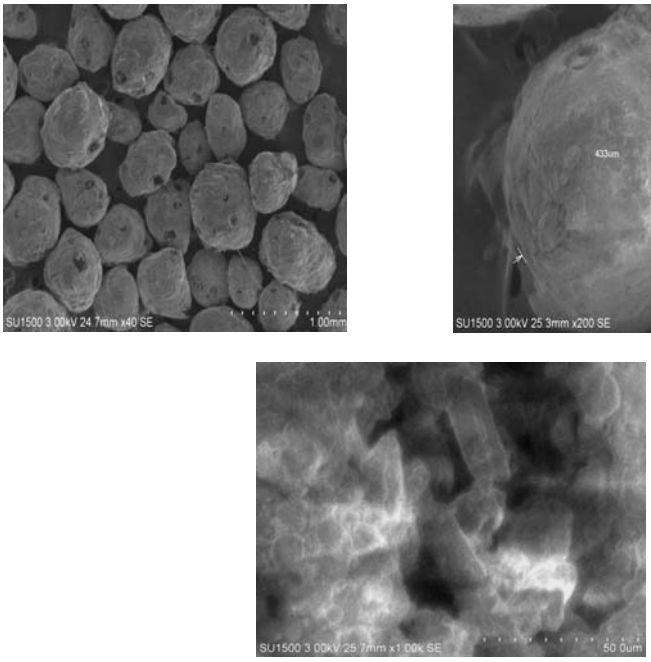
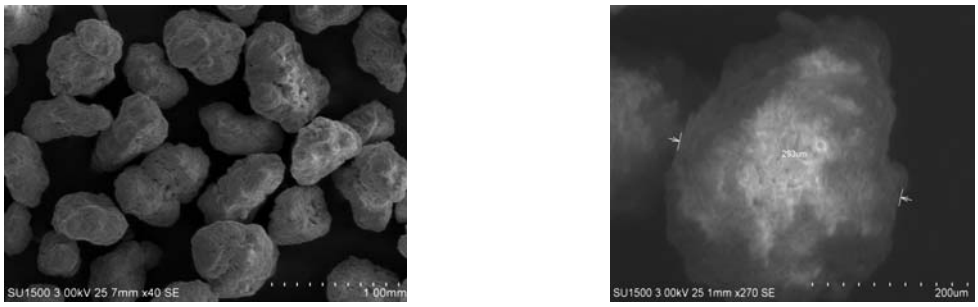


Fig. 4: SEM of ethyl cellulose microspheres of ondansetron



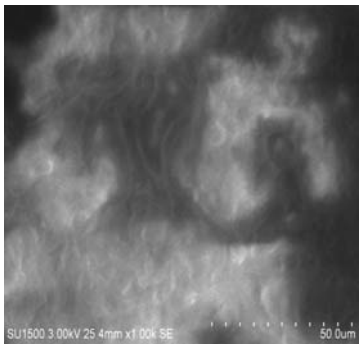


Fig. 5: SEM photographs of cellulose acetate phthalate microspheres of ondansetron

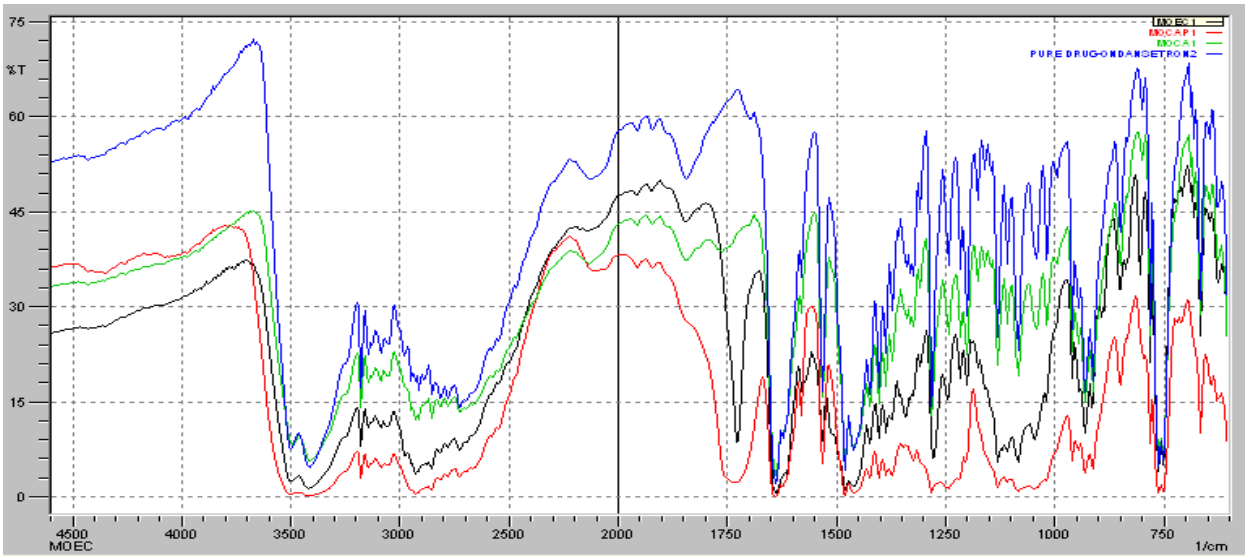


Fig. 6: IR Graphs of ondensetron Pure Drug, Drug+ EC, Drug+CAP and Drug+CA

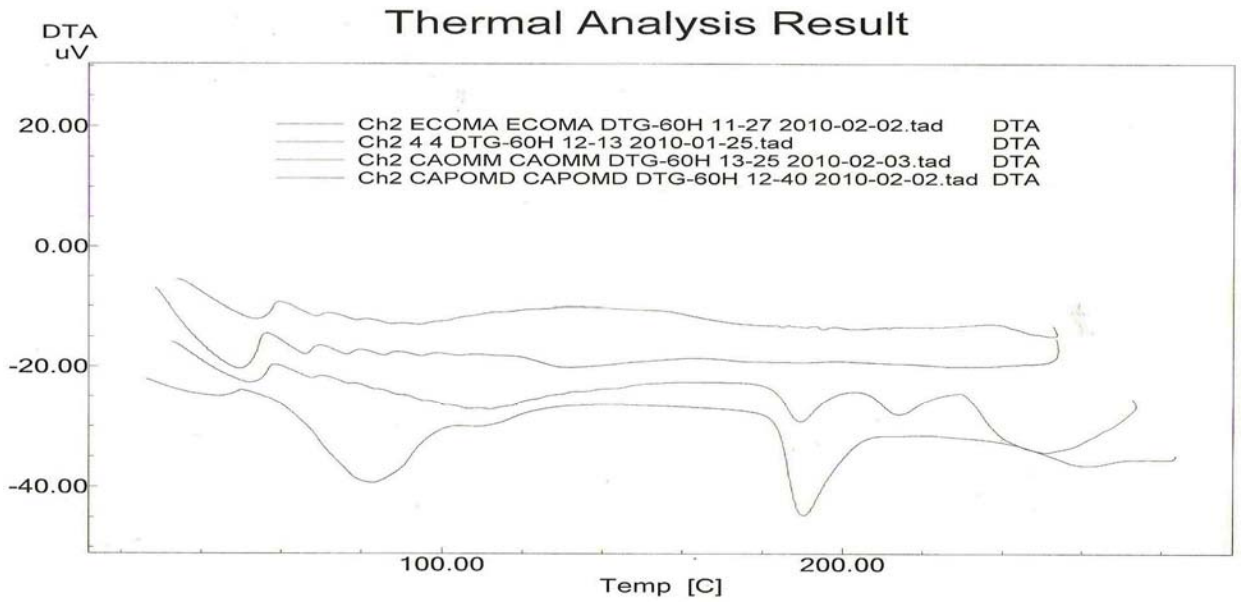


Fig. 7: TGA Graphs of ondensetron Pure Drug, Drug+ EC, Drug+CA and Drug+CAP

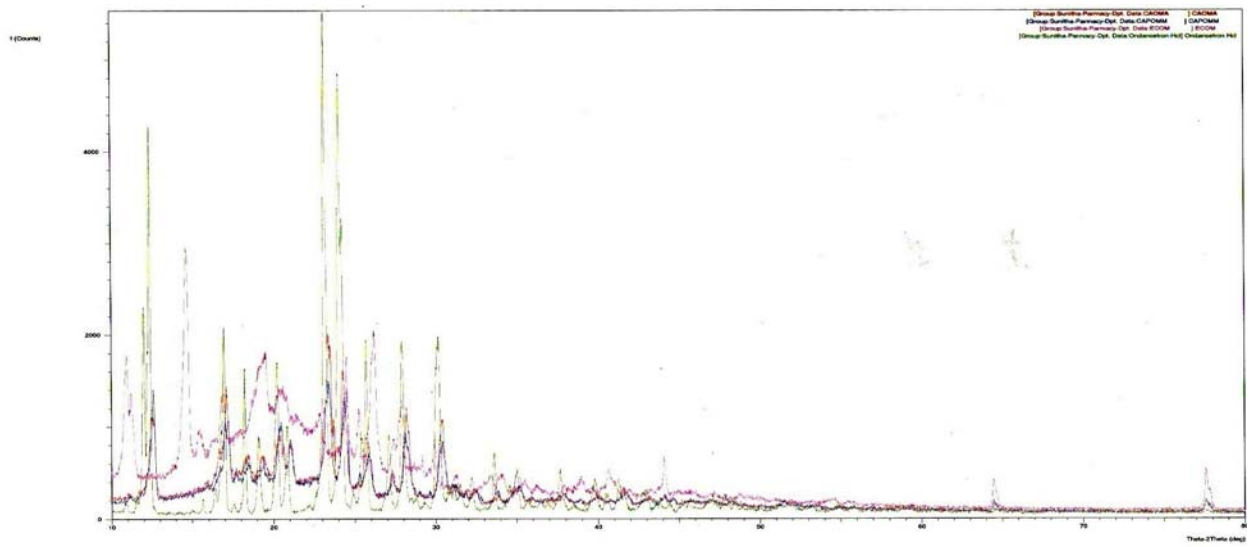


Fig. 8: XRD overlay graph of ondensetron Pure Drug, Drug+ EC, Drug+CA and Drug+CAP

CONCLUSION

The ondansetron hydrochloride microspheres sustained drug release for 12 hours or longer thereby it could be capable of reducing the frequency of administration and the dose-dependent side effects with the repeated administration of conventional ondansetron tablets. This type of sustained formulation will be better suitable for the cancer patients. No drug polymer interaction was found and formulations remained stable over a long period of time.

REFERENCES

1. Markham A, Sorkin EM. Ondansetron: an update of its therapeutic use in chemotherapy-induced and postoperative nausea and vomiting. Ind Drugs 1993; 45: 931-952.
2. Lachman L, Liberman HA, and Kanig JL. The Theory and practice of Industrial Pharmacy. 2nd ed. Philadelphia: Lea and Febiger; 1986. p. 412-29.
3. Ertan G *et al*. Sustained-Release microcapsules of Nitrofurantoin and Amoxicillin: Preparation, *in vitro* release rate kinetics and Micrometric studies. J Microencapsulation 1997; 14(3): 379-388.
4. Lie SP *et al*. Recent Advances in microencapsulation Technology and equipment. Drug Dev Ind Pharm 1988; 14(3): 353-376.
5. Hsyu PH *et al*. Comparision of the pharmacokinetics of ondansetron solution when administered intravenously, orally to the colon and to the rectum. Pharm Res 1994; 11: 156-159.
6. Hussain AA *et al*. Nasal absorption of ondansetron in rats: an alternative route of drug delivery. Cancer Chemother Pharmacol 2000; 45: 432-434.
7. Merkel HP, Speister P. Preparation and *in vitro* evaluation of cellulose acetate phthalate. J Pharm Sci 1973; 62(10): 1444-1448.
8. Othmer Kirk. Encyclopedia of chemical technology (volume-5). 3rd ed. New York: Wiley Interscience publication; 1979.
9. IBM, U.S. Patent, 3173878, 1965.
10. Beyger JW, Nair JG. Some factors affecting the microencapsulation of Pharmaceuticals with cellulose acetate phthalate. J Pharm Sci 1986; 75(6): 573-578.
11. Farid D, Nokhodchi. Dissolution of compacted aspirin microcapsules. Ind J Pharm Sci 1991; 53(5): 222-223.
12. Maharaj I, Nairn JG, Cambell JB. Simple rapid method for the preparation of enteric coated microcapsules. J Pharm Sci 1984; 73(1): 39-42.
13. Gene L *et al*. Microencapsulation of keterolac tromethamine by means of a coacervation phase separation technique induced by the addition of non-solvent. J Microencapsulation 1998; 15(1): 45-53.
14. Ndesendo VMK *et al*. Microencapsulation of chloroquine diphosphate by eudragits RS-100. J Microencapsulation 1996; 13(1): 1-8.
15. Pongpaibul Y *et al*. Preparation and *in vitro* dissolution of propanolol microcapsules. Int J Pharm Sci 1986; 33(1&3): 243-248.