Research & Reviews

Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences

Development of Fast Dissolving Tablets Containing Ondansetron via Camphor Sublimation and its Characterization

Rajnikant M Suthar[1]*, Narendra P Chotai[1], Digesh D Shah[2], Rutvik M Thumar[3], Hardik K Patel[1], Mukesh B Jadeja[4]

[1]AR College of Pharmacy and GH Patel Institute of Pharmacy, Vallabh Vidyanagar-388120, Anand, Gujarat, India. [2]Sanofi – Aventis Pharmaceuticals Ltd, Ankaeshwar, Gujarat, India. [3] Sahajanand Medical Technologies Pvt Ltd, Surat, Gujarat, India. [4]Shivam Pharmaceutical and Education Research, Anand, Gujarat, India.

Research Article

Received: 10/09/2012
Revised: 29/09/2012
Accepted: 01/11/2012

*For Correspondence:

AR College of Pharmacy and GH Patel Institute of Pharmacy, Vallabh Vidyanagar – 388120, Anand, Gujarat, India.
Email: rkpharma26@yahoo.co.in

Keywords: OSH, superdisintegrants, fast dissolving tablets, sublimation.

ABSTRACT

Ondansetron Hydrochloride (OSH) is a sparingly water-soluble drug. In this investigation fast dissolving tablets (FDTs) of ondansetron were prepared using different superdisintegrants by sublimation method. FDTs were evaluated for physicochemical properties and in vitro dissolution. The wetting time (10.5s) of formulation batch containing crospovidone (F2) was least and tablets showed fastest disintegration (3.2s). The drug release from FDTs containing superdisintegrants was more as compared to FDTs without superdisintegrant and it was found to be highest (98% drug release after 30 min) with formulation batch containing crospovidone (F2) so it can be concluded as promising formulation.

INTRODUCTION

OSH is an effective and well-tolerated anti-emetic, which is used for the prevention of both chemotherapy and radiotherapy-induced nausea and vomiting. OSH is sparingly soluble in water [1]. This fast dissolving tablet disintegrates instantaneously when placed on tongue and releases the drug dissolves or disperses in the saliva [2]. It is well absorbed from the gastrointestinal tract and undergoes first-pass metabolism. Mean bioavailability in healthy subjects, following oral administration of a single 8-mg tablet, is approximately 56%.

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 in case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance. To overcome these drawbacks, the concept of fast dissolving drug delivery system emerged from the desire to provide patient with conventional mean of taking their medication. Fast dissolving tablets are useful in patients[3,4],like pediatric, geriatric, bedridden, or mentally disabled, who may face difficulty in swallowing conventional tablets or capsules[5] leading to ineffective therapy[6,7],with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style.

Another approach used in developing such tablets is maximizing pore structure of the tablets by incorporating subliming agent like camphor menthol or thymol etc. in the sublimation technique. A porous hydrophilic matrix is generated which may easily pick up the disintegrating medium, break quickly and thereby provide instantaneous disintegration [7,8].

The aim of the proposed work was to formulate and characterize fast dissolving tablets of ondansetron by sublimation method for rapid dissolution of drug and absorption, which may produce rapid onset of action.

MATERIALS AND METHODS

Materials

OSH, Mannitol, aspartame, Croscarmellose sodium (CCS), Crospovidone (CP), Sodium starch glycolate (SSG), and Low substituted hydroxy propyl cellulose (L-HPC) were received from ZydusCadila 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 grade.

Preparation of Fast Dissolving Tablets

Ten batches of OSH FDTs were prepared by sublimation technique as per composition shown in Table 1. Mannitol, microcrystalline cellulose PH101, camphor and aspartame were passed through fine sieve before use. The excipients and drug were then 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). The tablet weight was adjusted to ~150 mg. Compressed tablets were subjected to the process of sublimation in vaccum oven at 60°C for 6 h.

Evaluation of Fast Dissolving Tablets [9]

Weight Variation

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

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[10,11].

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[12,13].

Mercury Porosimetry Studies and Surface Area Analysis

For mercury porosimetry, the sample was dried at 50°-60°C for 30-45 min; heating depends on the atmospheric condition. One tablet from promising batch was taken and porosity was measured using THERMOFINNIIGAN Model Pascal 140 series and Pascal 440 series. First sample was filled in to Model Pascal 140 series and filled up with the mercury. Pressure of 30 k pa was applied and slowly released that opened a big size pores. Then sample was loaded in Pascal 440 series and 380 k pa pressure was applied to cover smaller pores and finally pressure was released slowly. By combining both model data, pore size distribution was generated.

Scanning Electron Microscopy

Sample of one tablet (promising batch) was mounted on aaluminium stub and examined using a field emission, scanning electron microscope (Philips, ESEM, TMP+EDAX). Photographs were taken at magnification of 500X.

Drug Content

Ten tablets were crushed in mortar and powder equivalent to 8mg OSH was dissolved in sufficient quantity of distilled water and make up volume in 100 mL volumetric 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 (UV-1601, Shimadzu Corporation, Japan.). Each sample was analyzed in triplicate.

In vitro Dissolution Study

The dissolution of FDTs was carried out in paddle (USP type-II) apparatus. The dissolution media was 500 ml distilled water, maintained at 37 ± 0.5°C to permit the sink condition.[14] The rotation speed used 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.

Stability Studies

In the present work stability studies were carried out for selected formulation at room temperature (25°C ± 2°C/60% ± 5%RH) for 6 months. The formulation was evaluated for disintegration time, % drug content and % drug release.

RESULTS AND DISCUSSION

Evaluation of Fast Dissolving Tablets

The evaluation parameters are shown in Table 2. The hardness of tablets was found between 2.5 to 4.3 kg/cm^2. Friability of the tablets was found below 1% indicating good mechanical resistance of tablets. The drug content was found in the range of 95.14 – 98.21%.

The disintegration time of all the formulations was found in the range of 3.22-7.56s which was within official requirement as per FDA that is less than 30s. 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 – 14.12 s. From the results it has been found that FDTs containing CP as superdisintegrant (F2) showed fastest disintegration (3.22s) and least wetting time (10.5s) as compared to CCS, L-HPC, and SSG (Table-II).

Dissolution results shows that more than 90% drug released within 30 min from all batches containing supedisintegrants (F2 – F5) as compared to batch F1 without superdisintegrant (40% release). It can be inferred from the results that batch containing CP (F2) exhibited higher dissolution rate (98% release after 30 min) as compared to that of batch containing CCS, L-HPC, and SSG (F3-F5). The order for the superdisintegrants to enhance the dissolution rate could be ranked as CP> L-HPC> SSG> CCS. The comparative release profile is shown in Fig.1. F2 batch was selected as promising formulation because of higher drug release, fastest disintegration time and least wetting time.

Mercury porosimetry study was used to provide information on the bulk density and porous sublimed tablets, to propose a mechanism for fast disintegration/dissolution of sublimed tablets. It was found that porous sublimed tablet have surface area ranges from 16.508 – 25.68 m^2/g, the percentage porosity of prepared sublimed tablets were in the range of 22.87 – 29.49% (Table 3). Average pore diameter was in the range of 0.781 – 1.451 micron (Fig. 2) which might explain the very fast in vitro and in vivo disintegration as well as short wetting time obtained from sublimed tablets. Other parameters are shown in Table 3.

Scanning electron micrographs of the surface and cross section views of promising batch (F2) are shown in Fig. 3. The micrograph shows the highly porous nature of the prepared sublimed tablet, which appear in both surface and the inner structure. The highly porous nature of the tablet explains the rapid penetration of water, which results in rapid wetting, disintegration, and dissolution in the oral cavity[14].These results indicate that addition of camphor followed by sublimation greatly affected the inner structure of the tablet with subsequent impact on wetting, disintegration and dissolution of final tablet.

The results of stability studies revealed that there was no remarkable difference in the tested parameters of promising formulation after storage for 6 months (25°C ± 2°C/60% ± 5% RH) as compared to initial results (Table 4). The results of stability study demonstrated that the selected formulation was found to be stable.

CONCLUSION

In conclusion, fast dissolving tablets of Ondansetron prepared using crospovidone as superdisintegrant via camphor sublimation method seems to be promising formulation and further *in- vivo* study may be carried out.

Table 1: Compositions of Fast Dissolving Tablets Prepared by Sublimation Method

Ingredient	F1	F2 (CP)	F3 (L-HPC)	F4 (CCS)	F5 (SSG)
OSH	8 mg	8 mg	8 mg	8 mg	8 mg
Superdisintegrant	--	24 mg	24 mg	24 mg	24 mg
Microcrystalline cellulose PH-101	50 mg	50 mg	50 mg	50 mg	50 mg
Mannitol	80 mg	56 mg	56 mg	56 mg	56 mg
Aspartame	7.5 mg	7.5 mg	7.5 mg	7.5 mg	7.5 mg
Magnesium Stearate	1.5 mg	1.5mg	1.5 mg	1.5 mg	1.5 mg
Talc	3 mg	3 mg	3 mg	3 mg	3 mg
Camphor	20 mg	20 mg	20mg	20 mg	20 mg

Table 2: Results of Evaluation Parameters of Fast Dissolving Tablets Prepared by Sublimation Method

Evaluation Parameters	F1	F2	F3	F4	F5
Average weight of tablet (mg) (n=20)	152.05 (1.069)	150.84 (1.676)	151.18 (1.783)	152.45 (1.112)	151.67 (2.675)
Hardness(Kg/cm^2) (n=5)	3.0 (0.134)	4.3 (0.037)	2.8 (0.094)	3.0 (0.045)	2.5 (0.051)
Friability (%)	0.421	0.189	1.003	0.457	0.313
Disintegration time (sec) (n=5)	7.56 (0.428)	3.22 (0.161)	4.99 (0.175)	6.68 (0.306)	3.84 (0.114)
Wetting time (sec) (n=5)	14.12 (1.473)	10.50 (1.347)	14.49 (0.504)	22.59 (1.241)	11.45 (0.845)
% Drug content (n=10)	98.21 (1.551)	97.13 (1.126)	95.31 (1.511)	96.38 (1.683)	95.14 (1.311)
% Drug release after 30 min (n=3)	49.47 (0.713)	98.15 (1.383)	91.45 (0.911)	86.62 (0.845)	91.81 (1.729)

Values in parenthesis indicate Standard Deviations (n=3)

Table 3.Results of Mercury Porosimetry and Surface Area Analysis

Parameters	F2	F3	F4	F5
Total cumulative volume (cc/g)	0.299	0.293	0.243	0.257
Total specific surface area (m^2/g)	16.51	21.03	25.68	17.95
Average pore diameter (micron)	1.451	1.041	0.781	1.011
Total porosity (%)	29.49	28.15	22.87	27.72

Table 4:Results of Stability Studies of Promising Batch Initial and After 6 Months At 25°C ± 2°C/60% ± 5% RH.

Parameters	Promising Formulation (F2)	
	Initial	After 6 months
Disintegration time (Sec)	3.22 ± 0.161	3.83 ± 0.987
% Drug content	97.13 ± 1.126	96.67 ± 1.323
% Drug release after 30 min	98.15 ± 1.383	97.65 ± 2.546

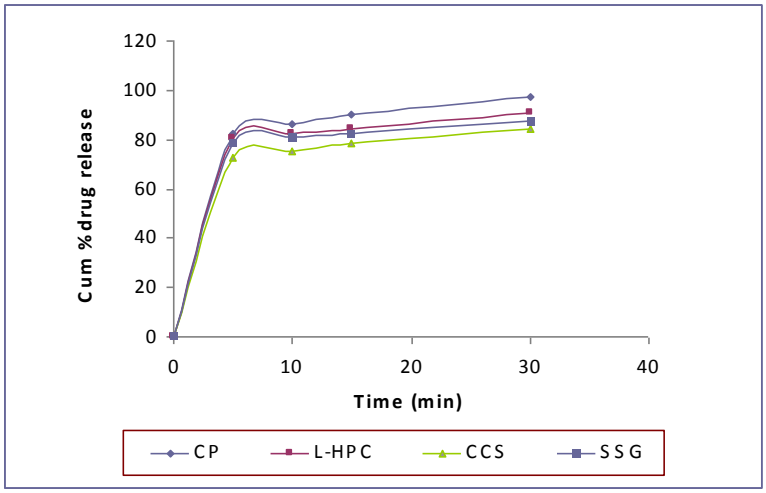

Figure 1.Comparative Release Profiles of FDTs with Different Superdisintegrants.

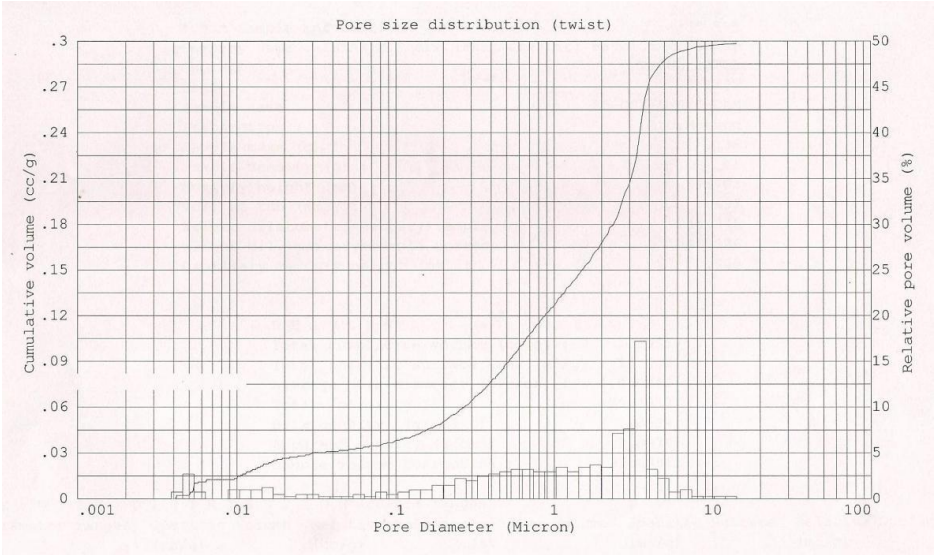

Figure 2.Porosity Analysis of Sublimed Tablets of Promising Batch (F2)

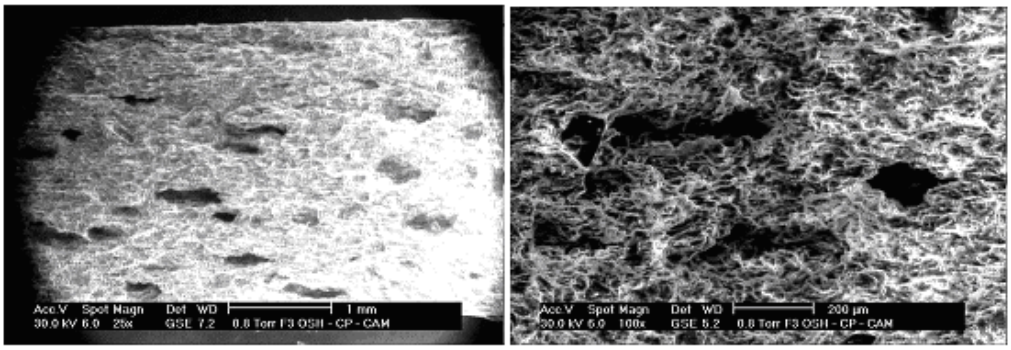

Figure 3. Scanning Electron Micrographs of FDTs in Surface View (A) and Cross-Section View (B).

ACKNOWLEDGEMENT

The authors would like to thank ZydusCadila Ltd., Ahmedabad, Relax Pharmaceuticals Ltd., Vadodara for providing gratis sample of drug and excipients.

REFERENCES

1. Salem I, Lopez K, Galan A, Florey K. Profiles of Drug substances and Excipients. Academic Press, California. USA 27 304-16.

2. Biradar SS, Bhagavati ST, Kuppasad IJ. Fast dissolving drug delivery systems: a brief overview. Int. J. Pharmacol 2006; 4(2):1531-2976.
3. Kaushik D, Dureja H, Saini TR. Mouth dissolving tablets: A review. Indian Drugs Bombay 2004; 41:187-93.
4. Chue P, Welch R, Binder C. Acceptability and disintegration rates of orally disintegrating risperidone tablets in patients with schizophrenia or schizoaffective disorders. Can J Psychiatry 2004; 49:701-3.
5. Shu T, Suzuki H, Hironaka K, Ito K. Studies of rapidly disintegrating tablets in oral cavity using coground mixture of mannitol with crospovidone. Chem Pharm Bull 2002; 50:193-8.
6. Seager H. Drug delivery products and the zydis fast dissolving dosage form. J Pharm Pharmacol 1998;50:375-8.
7. Chang RK, Guo X, Burnside BA, Couch RA. Fast dissolving tablets. Pharm Technol 2000; 24:52-8.
8. Habib W, Khankari R, Hontz J. Fast-dissolving drug delivery systems. Crit. Re. in Ther. Drug Carrier Systems2000; 17: 61-72.
9. Liberman HA, Lachman L. Pharmaceutical Dosage Form: Tablets.2nd Ed Inc. New York: Marcel & Dekker; 2005: 332-5.
10. Sammour OA, Hammad MA, Megrab NA, Zidan AS. Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersion. AAPS PharmSciTech. 2006; 7(2): Article 55.
11. Valleri M, Mura P, Maestrelli F, Ballerini R. Development and evaluation of glyburide fast dissolving tablets using solid dispersion technique. Drug DevInd Pharm 2004; 30(5): 525-34.
12. Gohel M, Patel M, Amin A, Agrawal R, Dave R, Bariya N. Formulation design and optimization of mouth dissolve tablets of nimesulide using vaccum drying technique. AAPS PharmSciTech 2004; 5: Article36.
13. Shoukri RA, Ahmed IS, Shamma RN. In vitro and in vivo evaluation of nimesulide lyophilized orally disintegrating tablets. Eur J Pharm Sci. 2009; 73(1): 162-71.
14. United States Pharmacopoeia 30, National Formulary 25, United State PharmacopeialConvection,Rockville 2007; 2149-2152.