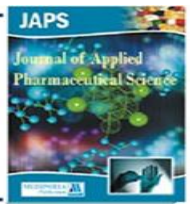
Journal of Applied Pharmaceutical Science
Available online at www.japsonline.com



ISSN: 2231-3354
Received on: 12-02-2012
Revised on: 29-04-2012
Accepted on: 01-05-2012
DOI: 10.7324/JAPS.2012.2517

Studies on directly compressed ondansetron hydrochloride mucoadhesive buccal tablets using gelatin, chitosan and xanthan gum along with HPMC K4M

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ABSTRACT

Mucoadhesive buccal tablets containing ondansetron hydrochloride (ODH) were prepared using polymers like gelatin, chitosan, xanthan gum in varying concentration of 5, 10, 15% w/w and HPMC K4M 40% w/w by direct compression technique. Precompressional studies revealed good micromeritic properties of powder blend for compression and were found as per literature limits. The prepared tablets were evaluated for thickness, hardness, uniformity of weight, drug content, friability, swelling index, mucoadhesion strength, *in vitro* disintegration, dissolution time and permeation studies. The formulations containing xanthan gum gave better mucoadhesion, release characteristics compared to those containing gelatin and chitosan and the rank order of mucoadhesion and permeation across sheep buccal mucosa was xanthan gum > chitosan> gelatin. The tablets apart from fulfilling all the official specifications, exhibited higher rate of release, *in vitro* release from all ODH buccal tablets followed Super case II transport due to polymer chain disentanglement and relaxation. and found to be stable upon conducting stability studies as per ICH guidelines at 40ºC/75 % RH. The results revealed that mucoadhesive buccal tablets containing ODH were successfully formulated by direct compression technique as an alternative to conventional tablets for therapy of nausea condition in patients.

Keywords: Buccoadhesive tablet, Ondansetron HCl, direct compression, stability studies.

INTRODUCTION

In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Drug delivery *via* the buccal route, using bioadhesive dosage forms offers such a novel route of drug administration. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity (Bhalodia *et al.*, 2010). The oral cavity is an attractive site for the administration of drugs because of ease of administration. Various dosage forms like Tablets, Capsules and Liquid orals are administered by oral route. In recent years, delivery of therapeutic agents through buccal mucosa has gained significant attention.

Administration of the drug via the mucosal layer is novel method that can render treatment more effective and safe. There are opportunities for local mucosal effect (Keiko *et al.,* 2002) and Transmucosal systemic effect (Calum *et al.,* 2002, Harikrishna *et al*., 2010) drug administration. The mucosal administration of drugs is to achieve site-specific release of drugs on the mucosa, whereas, in the latter, transmucosal administration involves drug administration through mucosal barrier to reach the systemic circulation (Silvia *et al.,* 2005, Prasad *et al.,* 2008, Shojaei *et al.,* 1998). Among the various transmucosal routes like nasal, rectal, vaginal, ocular, pulmonary and buccal routes (Yajaman *et al.,* 2006, Sevda *et al.,* 2001) the buccal mucosa is an attractive alternative to the oral route of drug administration and it is a potential site for the delivery of drugs to the systemic circulation (John *et al.,* 2001). Therapeutic agents administered through buccal mucosa enters directly to the systemic circulation and there by circumvent the first-pass hepatic metabolism, gastric irritation and other problems associated with conventional oral route. Among these the buccal mucosa has several advantages like excellent accessibility, an expanse of smooth muscle, immobile mucosa, moderate permeability, less enzymatic activity and suitable for the administration of retentive dosage forms (Vamshi *et al.,* 2007, Veuillez *et al.,* 2001, Pulak *et al.,* 2008). Moreover, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer therapeutic agent to patients who cannot be dosed orally to prevent accidental swallowing (Choy et al., 1999). ODH is a competitive Serotonin Receptor ($5HT_3$) antagonist. It is effective in the treatment of nausea and vomiting, has a half-life 3-5 h and oral bioavailability is < 60 %. ODH shows promising pharmacokinetics and physicochemical properties hence this drug was selected as model drugs for this investigation **(**Salem *et al.,* 2001, Anthony *et al.,* 2005). The literature revealed that there is very few methods reported for ODH buccal delivery as directly compressed tablets. Hence with this rationale the present study undertaken to investigate Preformulation studies of drug candidate, later buccal tablets of ODH was developed by direct compression and studied for pre, post compressional parameters, *in vitro* drug release profile through fresh bovine buccal mucosa. The tablets were also subjected for swelling studies, mucoadhesion and stability profiling.

MATERIALS AND METHODS

ODH was obtained as a complimentary sample from Anugraha Chemicals Bengaluru. Spray dried lactose was obtained as Complimentary Sample from Natco Ltd, Hyderabad. Chitosan was obtained as Complimentary Sample from Centrl Drug House, Mumbai. Xanthan gum from s.d. fine chem. limited. Mumbai and gelatin from Epson chemicals Enterprises. Mumbai.

Formulation of Mucoadhesive Buccal tablets containing ODH

Mucoadhesive tablets containing ODH were prepared by direct compression technique. The drug and the bioadhesive polymers, Xanthan Gum, Chitosan, Gelatin, HPMC K4M and Spray dried lactose as diluent as given in table 1 was taken; weighed individually and blended to fineness in a ball mill. Each powder was separately passed through sieve 100/120 and the undersized particles were used for further mixing. The powder beds were all taken into a cube mixer (Konark Labs, Haryana) and mixed for 10 min. After adequate mixing of drug as well as other components talc and magnesium stearate were added and further mixed for additional 3-5mins. The powder bed was studied for pre compressional parameters and then compressed into tablets on a 10 station rotary tablet press (PP1D, Chamunda) using 6 mm diameter, flat faced punches at a pressure of approximately 4- 6 kgs /cm^2.

Evaluation of ODH buccal tablets

Ten tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation. Hardness and friability of the tablets were determined by using Pfizer hardness tester and Roche friabilator respectively. From each batch three randomly selected tablets were weighed accurately and powdered in a clean and dry glass mortar with pestle. Powder equivalent to 100 mg of drug was transferred into 100 mL volumetric flask containing methanol; the remaining volume was made up to 100 mL with methanol. Shaken intermittently for 24 h and the solution was filtered, make up desired dilutions and analyzed for drug content at λ_{max} 212.5 nm, using a methanol as a blank. Triplicate readings were taken and average was computed. Disintegration test was performed for the prepared tablets in 900 mL, pH 6.8 at 37±2 ^oC by using USP disintegration apparatus. Time was noted with a digital chronometer. Triplicate readings were taken and average was computed. The various post compression characteristics evaluated for Mucoadhesive buccal tablets are illustrated in table no. 3 and 4.

Determination of swelling index

The swelling properties of the tablets were evaluated by determination of percent of swelling. Each tablet was weighed (W1) and immersed in a simulated saliva fluid at pH6.8 for predetermined times. After immersing the formulation for specified time, the tablets were wiped off to remove excess of surface water by using filter paper and weighed (W2) The %Swelling = (W2) – (W1)/ (W1)x100. Where, W 1 is the initial weight of the tablet and W2 is the weight of the tablet after the particular swelling time interval (Balamurugan *et al*., 2008).

Mucoadhesion strength

The equipment was fabricated by us in the laboratory. A double beam physical balance was taken, both the pans were removed. The left pan was replaced with a brass wire to which was hanged a polypropylene disc (A), also locally fabricated include an expanded cap another propylene disc was placed right below the suspended disc upon the base of the balance. The right pan (C) was replaced with a lighter pan so that the left pan weighs 9.5gm more than the right pan. The lower polypropylene block was intended to

hold the mucosal tissue (D) of bovine buccal mucosa and placed in a beaker containing pH 6.8(E). Fresh bovine buccal mucosa obtained from local slaughterhouse was cut into pieces, washed with distilled water followed by phosphate buffer pH 6.8. This buccal mucosa was placed over the surface of lower polypropylene cylinder (B) and secured this assembly was placed in a beaker containing pH 6.8 buffer at 37 ± 2^0c.

From each batch one tablet at a time was taken and stuck to the lower surface of upper polypropylene cylinder with a standard cyanoacrilate adhesive. The beaker containing mucosal tissue secured upon the lower cylinder (B) was manipulated over the base of the balance so that the mucosal tissue is exactly below the upper cylinder (A). The exposed part of the disc was wetted with a drop of buffer, then a weight of 15gms was placed was placed above the expanded cap, left for 15 minutes. After which the tablet binds with mucin, weight was removed.

Then slowly and gradually weights were added on the right side pan till the disc separates from mucosal surface/membrane. The weight required for complete detachment is noted (W_1gms). (W_1–9.5gms) gives force required for detachment, expressed weight in grams. Procedure was repeated for two more tablets and average was computed and recorded.

Surface pH study

The buccal tablet was allowed to swell by keeping it in contact with 1ml of distilled water for 2hr at room temperature. The pH was measured by bringing the pH-meter electrode, in contact with the surface of the tablet and allowing it to equilibrate for 1 min. The mean of three readings was recorded (Mahalaxmi *et al*., 2010).

***In vitro* Dissolution studies**

In vitro dissolution of mucoadhesive buccal tablets of ODH was studied in USP XXII type-II dissolution apparatus (DBK instruments, Mumbai) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 buffer at 37 ± 0.5º C as dissolution medium. Aliquots of dissolution medium (1 ml) were withdrawn at specified intervals of time and analyzed for drug content by measuring the absorbance at 212.5 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of ODH released was calculated and plotted against time (Balamurugan M *et al.,* 2008).

***In vitro* permeation studies**

In vitro drug permeation through the sheep buccal mucosa was performed using Keshary chien diffusion cell at 37±0.5°C. The freshly cut sheep buccal mucosa after removing underlying fat and loose tissues and washing with phosphate buffer pH 6.8 and distilled water was mounted between donor and receptor compartments. The receptor compartment was filled with phosphate buffer pH 7.4, and buccal mucosa was allowed to stabilize for 30 min in the receptor compartment by stirring on a magnetic stirrer at 50 rpm and was maintained for the entire study. A 1 ml aliquot was withdrawn at predetermined time intervals and replaced with fresh medium. The aliquots were analyzed after appropriate dilution by UV spectrophotometer (1700, Shimadzu) at 212.5 nm (Yamagar *et al.,* 2010).

Stability testing

The stability experiments were conducted to investigate the influence of temperature and relative humidity on the drug content and dissolution profile of various mucoadhesive buccal tablets. The formulations were exposed to a temperature of 40 °C and a relative humidity of 75 % RH. The sample was removed from the stability chamber at the end of 24 hours and the tablets were visually examined for any physical changes, analyzed for drug content for 90 days, and were subjected to dissolution study. Average of triplicate readings was taken. The observations were tabulated. The dissolution profiles were compared with dissolution profile performed on tablets kept at ambient conditions (Brain *et al.,* 1999).

Drug release kinetics

The *in vitro* drug release profiles were subjected for regression analysis and for kinetic study by zero order, first order and higuchi square root kinetics (Korsmeyer *et al.,* 1983).

Table. 1: Formulation chart of various ODH mucoadhesive buccal tablets.

S.no	Ingredients (mg/tab)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
1.	ODH	8	8	8	8	8	8	8	8	8
2.	Gelatin (5/10/15% w/w)	5	10	15	---	---	---	---	---	---
3.	Chitosan(5/10/15%w/w)	---	---	---	5	10	15	---	---	---
4.	Xanthan gum (5/10/15% w/w)	---	---	---	---	---	---	5	10	15
5.	HPMC K4M(40 % w/w)	40	40	40	40	40	40	40	40	40
6.	Talc and Mg. Stearate (2:1) 2 % w/w	2	2	2	2	2	2	2	2	2
7.	Spray Dried Lactose	45	40	35	45	40	35	45	40	35
Total Tablet Weight (mg)		100	100	100	100	100	100	100	100	100

Table. 2: Evaluation of rheological characteristics of ODH powder bed.

Formulation Code	Compressibility index %	Bulk density gm/ml	Tapped density gm/ml	Angle of repose (° θ)	
				Before glidant	After glidant
F1	13.6	0.454	0.526	30.96	23.96
F2	12.2	0.457	0.517	30.01	24.62
F3	12.8	0.457	0.521	30.65	28.61
F4	12.30	0.500	0.569	21.80	18.43
F5	14.2	0.489	0.576	29.24	26.56
F6	13.0	0.483	0.555	32.61	29.05
F7	12.5	0.491	0.561	34.9	29.87
F8	12.9	0.487	0.568	28.61	25.08
F9	13.4	0.459	0.530	26.05	19.79

Table. 3: Evaluation of post compression characteristics of ODH tablets.

Formula code	Weight (mg ±SD)	Hardness (kg/cm^2±SD)	Thickness (mm ± SD)	Drug content (mg ± SD)	Friability %
F1	105.4±6.32	5.7 ±0.115	3.15±0.002	7.804 ±0.001	0.16
F2	104.6±3.83	5.8±0.100	3.16±0.004	7.929 ±0.011	0.60
F3	102.2±2.25	5.83±0.152	3.14±0.004	7.612 ±0.017	0.49
F4	101.3±4.96	5.16±0.208	3.02±0.004	7.754 ±.0030	0.70
F5	104.9±6.24	5.66±0.115	3.06±0.004	7.75 ± 0.002	0.65
F6	103.6±3.71	5.06±0.115	3.06±0.004	7.945 ±0.006	0.80
F7	101.8±2.09	5.96±0.057	3.17±0.005	7.741 ±0.001	0.81
F8	101.1±1.28	5.90±0.100	3.13±0.005	7.925± 0.006	0.49
F9	100.8±1.54	6.00±0.010	3.18±0.005	7.916± 0.005	0.49

*Theoretical drug content = 8 mg

Table. 4: Swelling Index, mucoadhesive strength, Surface pH of ODH buccal tablets.

Formula code	Swelling index	Mucoadhesion Strength ± SD	Surface pH ± SD
F1	44.78	9.667±0.115	6.24 ±0.02
F2	55.22	12.133±0.208	6.60 ±0.09
F3	59.80	14.267±0.152	6.47 ±0.05
F4	39.48	15.200±0.450	6.70 ±0.03
F5	57.36	17.567±0.115	6.23 ±0.05
F6	66.30	21.500±0.500	6.52 ±0.01
F7	59.66	20.933±0.404	6.64 ±0.08
F8	72.77	23.000±0.500	6.57 ±0.04
F9	87.33	26.833±0.288	6.93 ±0.09

Table. 5: various kinetic parameters derived from *in vitro* studies of ODH buccal tablets.

Formulation	*In vitro* dissolution Studies				*In vitro* permeation Studies				
	Zero Order		Peppas		Flux mg/sqcm/h	D	Kp	Peppas	
	n	r	n	r				n	r
F1	0.866	0.997	1.709	0.926	0.112	0.0116	0.0015	1.258	0.917
F2	0.820	0.993	1.557	0.909	0.091	0.0093	0.0012	1.178	0.923
F3	0.753	0.975	1.737	0.931	0.074	0.0079	0.0010	1.134	0.917
F4	0.809	0.975	1.601	0.929	0.148	0.0154	0.0020	1.287	0.937
F5	0.791	0.992	1.328	0.867	0.113	0.0118	0.0015	1.237	0.931
F6	0.780	0.993	1.424	0.892	0.107	0.0109	0.0014	1.223	0.928
F7	0.979	0.997	1.652	0.913	0.163	0.0170	0.0022	1.328	0.935
F8	0.865	0.987	1.794	0.922	0.145	0.0148	0.0019	1.269	0.936
F9	0.842	0.982	1.818	0.983	0.133	0.0136	0.0017	1.252	0.934

RESULTS AND DISCUSSION

Mucoadhesive Buccal Tablets of ODH were prepared by direct compression technique using gelatin, chitosan and xanthan gum as mucoadhesive polymers and Spray Dried Lactose as diluent along with 40 % w/w HPMC K4M as binder. A total of nine formulations (F1 to F9) were designed and evaluated for various parameters. The tablet powder beds showed uniform and reproducible precompressional parameters indicated their free flowing and ease for compression as indicated in table 2. The average weight of the prepared tablets was in between 100.8 ± 1.54 mg to 105.4 ± 6.32 mg for a 100 mg tablet (n=10). The average thickness was found to be 3.02±0.004 mm to 3.17±0.005 (n=3).

The hardness of prepared tablets was found to be fairly consistent and uniform, ranging between 5.06 ± 0.115Kg/cm^2 to 6.0±0 Kg/cm^2 (n=3). The friability of all the formulations was less than 1% indicating the ability of tablet to withstand abrasion in handling packaging and shipment. The drug content of all the formulations having dose of 8 mg were found to be fairly uniform, reproducible and consistent, ranging between of 7.612 ±0.004 mg to7.945 ±0.01 mg for a tablet weighing 100 mg. The surface pH of the tablets, were found to be 6.23 ±0.05 to 6.93 ± 0.09 as represented in table 3. It was found that, increase in mucoadhesive polymer content increases the swelling index; indicated in figure 1 and Mucoadhesion strength of the tablet formulations.

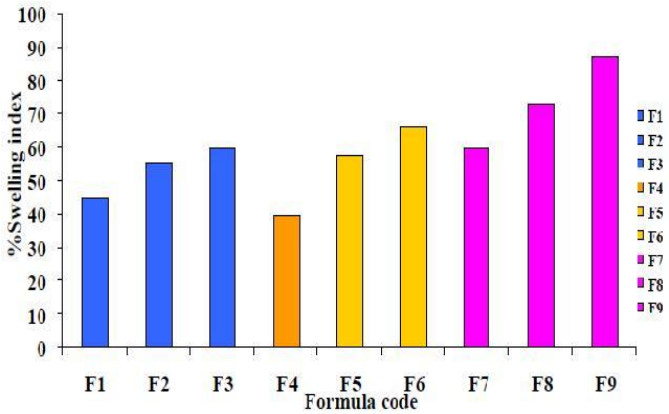

Fig. 1: Percent swelling index of ODH mucoadhesive buccal tablets.

The order of mucoadhesion strength was found to be F9> F8> F7 for tablets containing xanthan gum, F6> F5> F4 for tablets containing chitosan and F3>F2> F1 for tablets containing gelatin and the data was indicated in table 4.

As the content of mucoadhesive polymer in the tablet is increased, the rate of release figure 2 and permeation through sheep buccal mucosa is retarded as indicated by their flux values, obtained from slope of the curve figure 3. To ascertain the mechanism of release the data was plotted according to korsemeyer peppa equation the obtained results of kinetic analysis were given in table 5. Later it was found that, the release from the tablet follows Super case II transport owing polymer chain disentanglement and relaxation.

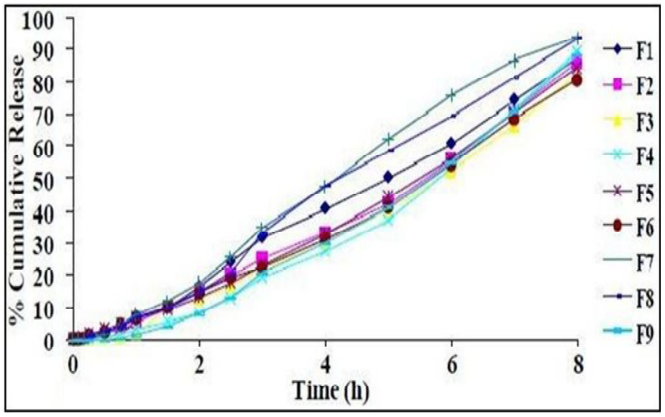

Fig. 2: Comparative *in vitro* drug release profiles of ODH from various mucoadhesive buccal tablets.

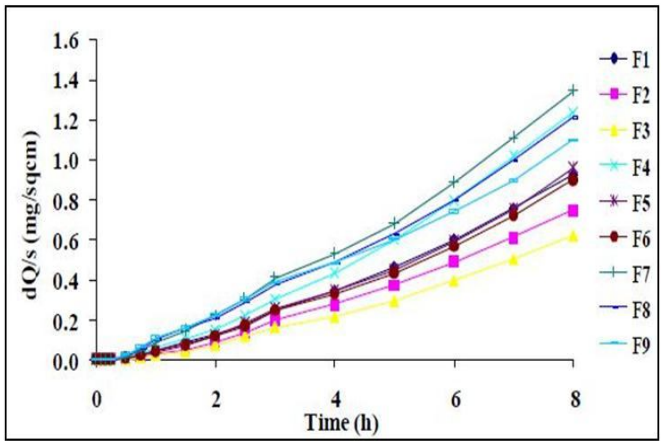

Fig. 3: *In vitro* flux of ODH from various mucoadhesive buccal tablets F1 to F9 across Sheep buccal mucosa.

CONCLUSION

Buccal formulations of ODH in the form of mucoadhesive tablets were developed to a satisfactory level, in terms of drug release, bioadhesive strength, content uniformity, swelling index, surface pH, friability, hardness and weight variation. Development of mucoadhesive buccal drug delivery of ODH is one of the alternative routes of administration to avoid first pass hepatic metabolism, improve bioavailability and sustain release. In this present study a formulation comprises of xanthan gum (F8 and F9) showed optimum drug release and satisfactory mucoadhesive properties. Thus the study revealed that the ODH buccal tablets showed good mucoadhesion time with sustained release of drug for 8 hours. The optimized formulation also showed satisfactory surface pH and physical parameters, effective *in vitro* permeation, satisfactory stability and comfort ability in the oral cavity. From the results of present investigation it can be concluded that ODH can certainly be administered through the oral mucosa and Xanthan gum is suitable for development of mucoadhesive system. Further work is recommended to support its efficacy claims by pharmacodynamic and pharmacokinetic studies in human beings. The manufactured fast dissolving tablets were found to be stable with respect to physicochemical and release characteristics at 40°C/75% RH after a period of 3 months. The results revealed that fast dissolving tablets containing ODH were successfully formulated by wet granulation technique as an alternative to conventional tablets.

ACKNOWLEDGEMENT

The authors are thankful to Dr. S. M. Shanta kumar Principal & management and staff of V.L. College of Pharmacy for providing necessary facilities to carry out the present research and also to Anugraha Chemicals Bengaluru and Natco Ltd, Hyderabad for providing complementary samples of active drug and excipients required for the study.

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