Research Article
CODEN (USA): IJPLCP

ISSN: 0976-7126
Sawant *et al.*, 11(7):6790-6796, 2020

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

Formulation and Evaluation of Oro Dispersible Tablets of Ondansetron Hydrochloride by Direct Compression using Superdisintegrants

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Article info

Received: 24/05/2020

Revised: 11/06/2020

Accepted: 25/07/2020

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Abstract

The objective of the present investigation was to prepare oro dispersible tablets of ondansetron hydrochloride, because of its application in emesis condition, fast onset of action and avoidance of water is highly desirable. Tablets were prepared by direct compression using sodium starch glycolate and croscarmellose as superdisintegrants, as the combination of these two agents gives better disintegration of the tablet. Microcrystalline cellulose was used as diluent and mannitol, mint flavor, sodium saccharine to enhance the organoleptic properties of tablets. The tablets were evaluated for weight variation, mechanical strength, *in vitro* disintegration time, *in vivo* disintegration time, wetting time, and drug release characteristics. Hardness and friability data indicated good mechanical strength of tablets.

The results of *in vitro* disintegration time and *in vivo* disintegration time indicated that the tablets dispersed rapidly in mouth within 3 to 5 seconds. Dissolution study revealed faster release rate of ondansetron hydrochloride from the tablets as compared to pure drug and marketed conventional tablet formulation of ondansetron hydrochloride. It was concluded that superdisintegrants addition technique is a useful method for preparing oro dispersible tablets by direct compression method.

Keywords: Oro dispersible tablets, super disintegrants, ondansetron hydrochloride, direct compression

Introduction

Most of the oral pharmaceutical dosage forms like conventional tablets and capsules are formulated to be swallowed or chewed. Elderly people and children sometimes have difficulties in swallowing these dosage forms. Such problem is more serious for bedridden patients. This problem is also applicable to active working or travelling people who do not have ready access to water (1). Recent advances in novel drug delivery system aims to provide rational drug therapy by enhanced safety and efficacy of drug molecule by formulating a convenient dosage form for administration and also by ensuring better patient compliance (2). One such approach is Oro Dispersible Tablets (ODTs). An ODT is a solid dosage form that disintegrates and dissolves in the mouth (either on or beneath the tongue or in the buccal cavity) without water within 60 seconds or less.

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The demand for ODTs has increased enormously during the last decade, particularly for geriatric and pediatric patients who have difficulty in swallowing conventional tablets and capsules (3) Research scientists have formulated ODTs of various categories of drugs like ibuprofen (4), lansoprazole (5), hydrochlorthiazide (6, 7), cefixime trihydrate (8), furosemide (9), nimesulide (10) and atenolol (11) which are used for therapy in which rapid peak plasma concentration is required to achieve desired pharmacological response.

The various technologies used to prepare ODTs includes freeze drying, tablet moulding, direct compression, spray drying, and sublimation (12). Direct compression represents a simple and cost effective tablet manufacturing technique. Use of conventional equipment, commonly available excipients and limited number of processing steps are the advantages of this technique. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrants, water soluble excipients and effervescent agents (13). The commonly used superdisintegrants are croscarmellose sodium (cross linked carboxymethylcellulose), crospovidone (cross linked povidone) and sodium starch glycolate (11). In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

Ondansetron hydrochloride is a selective 5-HT3 receptor antagonist (14). It is used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. It is also used for prevention of post operative nausea and vomiting in adults. Ondansetron hydrochloride is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single tablet, is approximately 56%.

The objective of the present investigation was to prepare ODTs of ondansetron hydrochloride, because in the emesis condition as well as in above mentioned specific conditions, fast onset of action and avoidance of water is highly desirable. The tablets were prepared by direct compression method using sodium starch glycolate and croscarmellose sodium as superdisintegrants. The combination of these two agents gives better disintegration of the dosage form and also does not adversely affect compressibility and flowability. Mannitol was selected due to its pleasant mouth feel property, good water dispersibility and binding property. It is also an effective tablet disintegrant and provides good hardness on compaction (10).

Material and Methods

Materials

Ondansetron hydrochloride (OSH) was a gift from Sun Pharmaceuticals Ltd., Vadodara. Microcrystalline cellulose (MCC), aspartame, mint flavour, croscarmellose sodium (CCS) were a gift from Astron Research Center, Ahmedabad. Sodium starch glycolate (SSG) (National Chemicals, Mumbai), mannitol (Hi Media Laboratory Limited, Mumbai), sodium saccharine (Loba Chemicals, Mumbai), Aerosil (S. D. Fine Chemicals, Mumbai), magnesium stearate (S. D. Fine Chemicals, Mumbai) were purchased.

Methods

Preparation of tablets by superdisintegrant addition technique

SSG and CCS were used as super disintegrants for preparation of ODTs of OSH by direct compression method. Various batches of tablet formulations prepared are shown in Table 1. Optimum combination was worked out based on powder blend properties and disintegration time of the tablets.

Preparation of powder blends for compression

Mannitol, SSG and CCS were passed through a 100 # screen prior to mixing. OSH was mixed to this blend of powder. Thereafter, mint flavour, aerosil, and magnesium stearate were added and mixed.

Evaluation of powder blend

Bulk density

Apparent bulk density (g/ml) was determined by placing pre-sieved bulk powder blend into a graduated cylinder via a large cylinder and measuring the volume and weight "as it is" (15).

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of powder on mechanical tapping apparatus, which was operated for fixed number of taps (around 250) until the powder bed volume reached a minimum. Using the weight of powder in a cylinder and this minimum volume, the tapped density was computed (15). From the results of bulk density and tapped density, Carr's index was calculated.

Angle of repose

For the measurement of angle of repose, a glass funnel was secured with its tip at a given height (H) above a piece of graph paper placed on a horizontal surface. Powder was poured through the funnel until the apex of the conical pile touched the tip of the funnel. The angle of repose was calculated with the formula tan a = H/R, where a, is the angle of repose and R is the radius of the conical pile (15).

Table 1: Composition of ODTs of Ondansetron HCl

Batches/ (mg/ tablet)	S_1C_0	S_0C_1	S_1C_1	S_2C_2	S_4C_2	S_2C_4	S_4C_0	S_0C_4
Ondansetron HCl	4	4	4	4	4	4	4	4
SSG	1	--	1	2	4	2	4	--
CS	--	1	1	2	2	4	--	4
Mannitol	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6
MCC (Avicel 102)	61.4	61.4	60.4	58.4	56.4	56.4	58.4	58.4
Sodium Saccharine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mint Flavour	2	2	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1	1	1
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Compression of tablets

The powder blends prepared for different batches were compressed into flat tablets, 80 mg in weight, and 5.5 mm in diameter, by using rotary tableting machine (General Machinery Limited, India)

Evaluation of tablets

Uniformity of weight (Weight Variation)

Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

Hardness

The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was determined using a Monsanto hardness tester (1) (Sheetal Scientific Industries, Mumbai, India).

Friability

Friability of tablets was measured by using Roche Friabilator (16) (Electrolab, Mumbai, India). Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a friabilator at 25 rpm for 4 minutes. The tablets were dedusted, and the loss in weight caused by fracture or abrasion was recorded as the percentage weight loss. Friability below 1% was considered acceptable.

***In-vitro* disintegration time**

The disintegration time was measured using a paddle method originally proposed by Sunada et al (18). The assembly utilizes dissolution apparatus USP XXIII paddle apparatus (Electrolab, TDT-06T, Mumbai, India). The vessel was filled with 500 ml of water maintained at 37 °C. The paddle was rotated at 100 revolutions per minute. The tablet was placed inside the sinker and the time at which it passes completely through the mesh of sinker was taken as the disintegration of the tablet.

***In vivo* disintegration time**

Measurements of disintegration time in the mouth were carried out in six volunteers. After the mouth was rinsed with purified water, one tablet was held in the mouth until the tablet disintegrated without chewing and then spat out, and the mouth was rinsed again. The disintegration time was recorded.

Wetting time

The wetting time of the tablets was measured using a simple procedure (20). Five circular tissue papers of 10-cm diameter were placed in a petri dish with a 10-cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.

Wetting volume

The tablet was placed in the center of the petri dish and with the help of 5 ml pipette, distilled water was added drop wise on the tablet. The volume required to completely disintegrate the tablet was noted as the wetting volume.

Dissolution study

The dissolution study was performed for pure drug OSH, batch S C and marketed conventional tablet formulation by using USP XXIII paddle apparatus (Electrolab, TDT- 06T, Mumbai). The dissolution medium was distilled water (900 mL, 37 ± 0.5 C). The rate of agitation of the paddle was 50 rpm. Aliquot of dissolution medium was withdrawn at specific time interval of 5 minutes, it was filtered and absorbance was measured spectrophotometrically at 310 nm by UV spectrophotometer (UV-1601, Shimadzu Corporation, Kyoto, Japan).

Results and Discussion

The present investigation was undertaken to formulate and evaluate oro dispersible tablets of ondansetron hydrochloride by direct compression method using sodium starch glycolate and croscarmellose sodium as superdisintegrants. Superdisintegrants are generally used by formulation scientists for developing ODTS or for improvement of solubility for active pharmaceutical ingredients. The primary requirement for both dosage forms is quicker disintegration. The results obtained by evaluating the powder blends of drug and excipients is shown in Table 2. The two most important attributes for the direct compression formula are good flow and good compressibility (21). The values obtained for bulk density and tapped density does not affect the compression of tablets. The angle of repose gives important information about the flow characteristics of the powder mixture. The powder flow depends on three general areas: the physical properties of the particle (e.g., shape, size, compressibility), the bulk powder properties (e.g., size distribution, compaction); and the processing environment (e.g., storage, humidity) (22). The angle of repose <30° indicates free flowing material and >40° with poor flow properties (16). Values for angle of repose were found in the range of 24 to 28° showing that the blend of powder was free flowing and can be used for direct compression. The value for Carr's index was in between 0.82-0.88 (<1), indicating that all the batches of powder blends were having good compressibility.

Table 2: Evaluation of Powder Blends of Ondansetron HCl and Excipients

Formulations	Bulk Density* (gm/ml)	Tapped Density* (gm/ml)	Angle of Repose* (^{0})	Carr's Index
S_1C_0	0.58±0.067	0.66±0.075	27.06±1.67	0.82
S0C1	0.57±0.097	0.66±0.084	27.09±1.34	0.86
S_1C_1	0.56±0.057	0.65±0.046	26.57±1.56	0.86
S2C2	0.58±0.057	0.66±0.076	24.62±0.89	0.87
S4C2	0.6±0.034	0.69±0.027	24.42±1.64	0.86
S_2C_4	0.61±0.046	0.69±0.064	24.17±1.75	0.88
S4C0	0.67±0.047	0.67±0.047	24.51±1.42	0.85
S0C4	0.58±0.023	0.66±0.087	24.49±1.63	0.87

* The data are expressed as mean±S.D. (*n*=3).

ISSN: 0976-7126
Sawant *et al.*, 11(7):6790-6796, 2020

Table 3: Evaluation of ODTs of Ondansetron HCl

Formulations	Weight Variation* (%)	Hardness* (Kg/cm^2)	Friability* (%)	*In vitro* Disintegration Time (seconds)	*In vivo* Disintegration Time (seconds)
S_1C_0	5.7±0.51	3.2±0.39	0.5±0.14	52 – 58	60 – 66
S_0C_1	6.0±0.22	3.2±0.67	0.7±0.12	65 – 70	62 – 68
S_1C_1	5.5±0.34	3.0±0.46	0.6±0.25	58 – 60	60 – 65
S2C2	5.0±0.28	3.0±0.69	0.63±0.15	3 – 5	3 – 4
S4C2	5.4±0.30	3.0±0.59	0.6±0.17	3 – 5	3 – 4
S_2C_4	5.0±0.54	3.0±0.34	0.7±0.13	5 – 7	4 – 5
S4C0	5.2±0.28	3.0±0.76	0.6±0.21	32 – 35	25 -27
S0C4	5.0±0.39	3.0±0.94	0.6±0.16	38 - 40	30- 34

* The data are expressed as mean±S.D. (*n*=3).

Table 4: Dissolution profile for pure drug Ondansetron HCl, prepared ODT batch S_2C_2 and marketed conventional tablet formulation

Time (minutes)	Cumulative percentage drug release*		
	Pure drug	Batch S_2C_2	Marketed conventional tablet formulation
5	2.0±0.12	87.502.27	0.0
10	2.0±0.38	89.05±2.18	2.3±0.42
15	8.0±0.25	91.13±2.76	4.2±0.58
20	15.0±0.15	93.48±3.61	13.6±0.35
25	20.0±0.27	95.96±4.21	20.4±0.14
30	26.0±0.35	98.63±2.47	39.5±0.34

* The data are expressed as mean±S.D. (*n*=3).

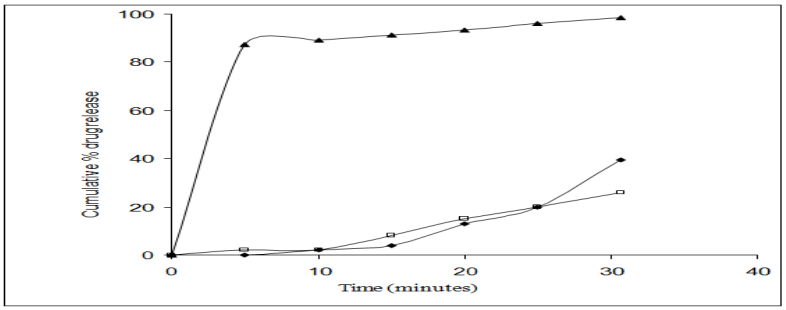

Fig.1: *In vitro* drug release for pure drug Ondansetron HCl (□), prepared ODT batch S_2C_2 (▲) and marketed conventional tablet formulation

The results for evaluation of different batches of ondansetron hydrochloride ODTs prepared by direct compression method are shown in Table 3. Percent weight variation was observed between 5.0 and 5.7 which were well within the acceptable limit for uncoated tablets as per United States Pharmacopoeia. One of the primary requirements of immediate release preparation is faster disintegration. It is well known to formulation scientists that the tablets with higher crushing strength show longer disintegration time. Since mechanical integrity is of paramount importance in successful formulation of ODTs, hence the hardness of tablets was determined and was found

to be in the range of 3.0 to 3.2 Kg/cm . Friability was observed between 0.5 to 0.7%, which were below 1% indicating sufficient mechanical ingregity and strength of prepared tablets. Thus, hardness and friability data indicates good mechanical resistance of tablets. *In vitro* and *in vivo* disintegration time for different batches of ODTs was 3 to 70 seconds and 3 to 68 seconds respectively. The tablet formulations containing SSG and CCS alone at low concentration (1 mg/tablet) showed higher values of 52 to 70 seconds for *in vitro* and *in vivo* disintegration time. The *in vitro* and *in vivo* disintegration time for formulations containing low concentration of 1 mg/tablet for both the super disintegrants in combination was observed to be 58 to 65 seconds. The formulations containing 2mg of SSG and CCS in combination per tablet showed 3 to 5 seconds value for *in vitro* and *in vivo* disintegration time. When the amount of SSG and CCS was increased up to 4 mg per tablet without combination, the values for *in vitro* and *in vivo* disintegration time was observed in between 25 to 40 seconds. This result of *in vitro* and *in vivo* disintegration time indicates that the batch S_2C_2 containing 2mg/tablet of SSG and CCS showed minimum time of 3 to 5 seconds to disintegrate *in vitro* and *in vivo*. Hence the batch S_2C_2 was used for further studies like wetting time, wetting volume, dissolution profile study.

Wetting time was determined to get idea of wetting lag time before disintegration. The wetting time for batch S2 C2 was 2 seconds. The wetting volume is important to check minimum volume of water required for wetting of tablet. The wetting volume for batch S_2C_2 was 0.29±0.03 ml, which shows that very small amount of water is required for wetting of tablet. It has been reported that wetting is closely related to the inner structure of the tablets and the hydrophilicity of the excipients. SSG and CCS show its disintegrant effect by the mechanism of swelling (21). Thus these results indicate that these tablets would disintegrate almost instantaneously when they will come in contact with even slight quantity of saliva in the mouth.

The cumulative percentage drug release from pure drug, prepared ODT batch S_2C_2 and marketed conventional tablet formulation is shown in Table 4. It was observed that in first 10 minutes, only 2.0 % drug was released from pure drug and marketed conventional tablet formulation while it was 89.0 % in case of ODT. At the end of 30 minutes, 98.0

% of drug was released from the batch S_2C_2 as compared to pure drug and conventional tablet formulation in which only 26.0 % and 39.5 % drug was released respectively (Figure 1). Thus the release rate of ondansetron hydrochloride was significantly enhanced by formulating ODTs by using superdisintegrants.

Conclusion

Oro dispersible tablets of ondansetron hydrochloride were prepared by direct compression method using sodium starch glycolate and croscarmellose sodium as superdisintegrants. The tablets disintegrated rapidly in oral cavity and had acceptable hardness and friability. *In vitro* drug release from the tablets shows significantly improved drug dissolution. Hence it could be concluded that the superdisintegrant based oro dispersible tablets of ondansetron hydrochloride would be quite effective in emesis, providing quick onset of action without need for water for swallowing or administration.

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Cite this article as:
Gosai A.R., Patil S.B. and Sawant K. K. (2020). Formulation and Evaluation of Oro Dispersible Tablets of Ondansetron Hydrochloride by Direct Compression using Superdisintegrants, *Int. J. of Pharm. & Life Sci.*, 11(7): 6790-6796.
Source of Support: Nil
Conflict of Interest: Not declared
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