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Research Article

Development and Evaluation of Ondansetron Orally Disintegrating Tablets

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ABSTRACT

Orally disintegrating tablet (ODT) has number of advantages like faster onset of action, ease of administration, rapid disintegration and dissolution etc. A novel attempt has been made to develop orally disintegrating tablets of Ondansetron by using two approaches, one is soluble hydrophilic matrix by superdisintegrant and other is effect of sweetener on the formulation. Direct compression method was employed for making orally disintegrating tablets. The formulated orally disintegrating tablets have rapid disintegration property for better patient compliance. Formulated tablets were evaluated for physical parameters along with wetting time, disintegration time, drug content and "in vitro" dissolution. In first approach it was found that batch F7 containing Crospovidone (Polyplasdone XL 10) 10 mg showed minimum disintegration time (i.e. approx. 7.00 seconds) with maximum drug release. Wetting time for batch F7 was found to beminimum (i.e. 12 seconds). In second approach of selection of sweetener batch F 10 containing Sodium saccharin was found better in terms of Impurity study (Relative Substances study).Impurity was found within the specified limit compared to other two sweeteners. Stability study was carried out on optimized formulation. Overall batch containing 10 mg Crospovidone (Polyplasdone XL 10) along with Sodium Saccharin was foundstable both physically and chemically.

INTRODUCTION

Over the last decade, the demands for more patients-friendly dosage forms are growing. As a result, the demand for developing new technologies is increasing day by day. As the cost of development of new drug molecule is very expensive, pharmaceutical companies are now focusing mostly on development of new dosage forms of same existing drugs which have better safety and efficacy, reduced dosing frequency and most importantly production friendly and cost effective (Hirani, Rathod et al. 2009).

Oral route of drug administration have greatacceptance around 50-60 % of total available dosage forms of same drug. Accurate dosing, self-medication, pain avoidance and most important patient convenience are characteristics of solid oral dosage forms that make them popular (Sreenivas, Dandagi et al. 2005).

ODTs are one of the popular dosage form which has been designed for rapid disintegration when comes in contact with saliva. ODTs help the patient to administer formulation without cup of water or chewing. Geriatric population are facing the problem

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of swallowing, in such cases ODTs have a potentialto increase the patient compliance (McLaughlin, Banbury et al. 2009).

As per United States Food and Drug Administration (USFDA) Regulation orally disintegrating tablet defined as "A solid dosage form containing medicinal substances which disintegrates rapidly, almost within seconds, when it comes in contact withsaliva placed upon the tongue (Ölmez and Vural 2009). Orally disintegrating tablets (ODT) are also called as orodispersible tablet, quick-dissolving tablet, fast-melt tablets, mouth-dissolving tablet and rapid disintegrating tablets (Pfister and Ghosh 2005).

Some patients suffer from critical buccal conditions involving difficulty in swallowing tablets and capsules and thus leading to problems in administration of oral medicine forms. These conditions are known as "dysphagia", a general term meaning difficulty in swallowing or more particularly "odynophagia", meaning painful swallowing, in such condition orally disintegrating tablet (ODT) have better advantages (Costantini 2011).

The need to take conventional pharmaceutical tablets with the aid of fluid can be inconvenient or impractical. For example, it can be difficult to administer conventional pharmaceutical tablets to a paediatric, geriatric, or psychiatric patient. Orally disintegrating tablet has received a lot of interest because they disintegrate or dissolve rapidly in saliva, therefore,may eliminate the need to swallow with the aid of fluid (Dong 2013).

Orally disintegrating tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx & also fromoesophagus as the saliva passes down from mouth into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form (Kaur, Gill et al. 2011).

Ondansetron is a very potent and highly selective 5HT3 (5-hydroxytryptamine) receptor antagonist drug. Exact Mechanism of action which controls nausea and vomiting is not known. It is assumed that chemotherapeutic agents and radiotherapy releases 5HT in the small intestine which initiating a vomiting reflex by activating vagal afferents via 5HT3 receptors. Possibly Ondansetron may block the initiation of this reflex. Sometimes activation of vagal afferents may cause release of 5HT in the area postrema, which has been located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, Ondansetron is effective in the management of the nausea and vomiting induced by chemotherapy and radiotherapy which is possibly due to antagonism of 5HT3 receptors on neurons located in peripheral as well as central nervous system. The exact mechanism of action in post-operative nausea and vomiting are also not known but there may be common pathways with cytotoxic induced nausea and vomiting (MHRA 2007).

Ondansetron is typically administered via oral route prior at start of chemotherapy or radiotherapy or surgery in order to have an immediate effect. In some cases nausea and vomiting discomforts the patient to take medicine along with fluid hence orally disintegrating tablet is the choice (Venkatesh 2011). The US patent US7390503 B1 claims formulation of Ondansetron ODT using lipophilic cellulose derivative, tablet disintegrants containing —CHOH functional group and a lubricant (Gorukanti et al. 2008).

The European patent EP 2506714 A1 claims preparation of ODT containing weak basic drug Ondansetron for the sake of patient compliance in the treatment of nausea and vomiting (Venkatesh 2011).

MATERIALS AND METHODS

Materials

Ondansetron (API), Mannitol (Perlitol SD200), Microcrystalline cellulose(PH 102), Crospovidone (Polyplasdone XL10), Sodium starch glycollate, Croscarmellose sodium , Sodium saccharin, Sucralose, Acesulfame potassium, Colloidal Silicon Dioxide, Colour lake of Erythrosine, Peppermint DM9140, Magnesium stearate were procured from Zuventus Healthcare Ltd. Pune (Holm, Allesø et al. 2017).

Drug-Excipient Compatibility Study

Drug excipient compatibility study was performed by mixing drug with individual excipient in the ratio 1:1,

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then this mixture was filled in respective labelled clear vials, sealed and kept for 15 days in stability chambers at 25°C / 60%RH, 40°C / 75%RH & 60°C. After 15 days, these vials were examined for physical appearance, colour, nature of mixture, FTIR and impurity profile study. (Holm, Allesø et al. 2017)

Formulation Development

Formulation was evaluated with two different approaches i.e. using Superdisintegrants and Sweeteners. The design was selected on the basis of optimum disintegration time and other evaluation parameter. Formulation design for selection of Superdisintegrants is given in Table 1 and the same for selection of sweeteners is given in Table 2.

Table 1 *Formulation design for selection of Superdisintegrants.*

Formulations/Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ondansetron	04.05	04.05	04.05	04.05	04.05	04.05	04.05	04.05	04.05
Mannitol (perlitol SD200)	36.50	36.50	36.50	36.50	36.50	36.50	36.50	36.50	36.50
Microcrystalline cellulose(PH 102)	34.40	36.90	39.40	34.40	36.90	39.90	34.40	36.90	39.40
Sodium starch glycollate	10	7.5	5	-	-	-	-	-	
Croscarmellose sodium	-	-	-	10	7.5	5	-	-	-
Crospovidone (Polyplasdone XL10)	-	-	-	-	-	-	10	7.5	5
Colloidal Silicon Dioxide	2	2	2	2	2	2	2	2	2
Peppermint DM9140	2	2	2	2	2	2	2	2	2
Colour lake of Erythrosine	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total	90	90	90	90	90	90	90	90	90

Manufacturing Procedure

Initially sifted through 40# sieve Ondansetron, Mannitol (Pearlitol SD200), Microcrystalline (PH102), Colloidal silicon dioxide, Peppermint flavour DM 9140, Superdisintegrating agent and Sweetening agent. The above sifted contents were mixed in octagonal blender for 30 mins. Magnesium stearate was sifted through 60 # sieve and added to above step and mixed in octagonal blender for 5 minute. Compressed the tablets as per given parameters (Table 3).

Evaluation of Tablets

Weight Variation: Twenty tablets were selected randomly and weighed individually. Average weight of the tablets was determined. Deviation of each tablet weight from average weight was determined. The specification used for weight variation test was as per IP (NMT 7.5%), (Pharmacopoeia 2018a).

Thickness: Thickness in mm was measured by using Vernier Callipers.

Tablet hardness: The hardness was measured by using "Pharma Test hardness tester" in terms of kg/cm2.Average of 10 tablets were measured (Liberman and Kanig 1987).

Friability: Friability is the measure of resistance to abrasion and of shock resistance. Roche friabilator was used for testing the friability using the following procedure.

Approximately 6.5 gm tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 100 rotations, the tablets were weighed and the percentage loss in tablet weight was determined. (Pharmacopoeia 2018a; Liberman and Kanig 1987).

Table 2. *Formulation design for selection of Sweeteners.*

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Formulation Ingredients	F10 (mg)	F11(mg)	F12(mg)
Ondansetron	04.05	04.05	04.05
Mannitol (Perlites SD200)	36.50	36.50	36.50
Microcrystalline cellulose (PH 102)	32.40	32.40	32.40
Crospovidone (Polyplasdone XL10)	10	10	10
Sodium saccharin	2	-	-
Sucralose	-	2	-
Acesulfame potassium	-	-	2
Colloidal Silicon Dioxide	2	2	2
Colour lake of Erythrosine	0.05	0.05	0.05
Peppermint DM9140	2	2	2
Magnesium stearate	1	1	1
Total	90	90	90

Table 3. *Compression parameters for the tablets.*

Parameters	Standards
Punch	6.5 mm FFBE, round shape punch with breakline on upper punch and plain on lower punch.
Description	Light Pink colour, round shaped, flat face, bevelled edge uncoated tablets with breakline on one side & plain on other side.
Average weight (mg)	90.00 mg
Hardness (kg/cm^2)	NLT 2.0
Thickness (mm)	2.80
Disintegration time (Min.)	NMT 30 seconds
Friability(%)at 200 rotations	NMT 1

Disintegration time: Disintegration time was calculated on DT apparatus. 6 units were selected randomly and placed in each basket and machine was started. The time at which complete tablet get disintegrated was recorded as disintegration time of the tablet(Liberman and Kanig 1987, Pharmacopoeia 2018)

Wetting time: The method was applied to measure tablet-wetting time. A piece of Whatman filter#41 paperfolded once diametrically was placed in a small petridish (i.e. = 6.5 cm) containing 8 ml of water, a tablet was put on the paper, and the time for complete wetting was measured. (Pabari and Ramtoola 2012)

"In vitro" dispersion test: "In vitro" dispersion time was measured by dropping two tablets in a 100 ml flask containing of distilled water with stirring. Stirring was done with the help of mechanical stirrer with the speed of 500 RPM and time 10 minutes.Then this solution passes through 710um sieve (Kuchekar, Badhan et al. 2004).

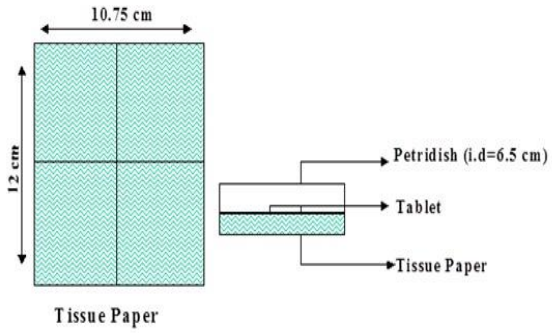

Figure No.1 *Simple method for the measurement of wetting time of a tablet (Nagendrakumar, Keshavshetti et al. 2015).*

"In vitro" drug release studies: The "in vitro" drug dissolution studies of prepared orally disintegrating tablet of Ondansetron were studied using USP apparatus II (paddle). 500 ml, 0.1 N HCl was used as dissolution medium. Orally disintegrating tablet were placed in a vessel and rotated at a speed of 50 rpm, maintained at a temperature 37°C ± 0.50°C. For the determination of "in vitro" drug release of the drugs, 10 ml aliquots from each vessel were pipetted out at the end of 10 minute, filtered through Whatman filter paper no. 41 and analysed over Schimadzu UV – 1601 spectrophotometer at 310 nm (Pharmacopoeia 2018b).

Assay: Assay of Ondansetron orally disintegrating tablets was calculated by using method specified in Indian pharmacopoeia (Pharmacopoeia 2018b).

Related substances: Related substances study was carried out on the formulation as per Indian Pharmacopoeia. As per IP there are two specified impurities namely 2-Methylimidazole and Ondansetron impurity Dither test was performed by using liquid chromatography. The limit of area of the peak for the 2-Methylimidazole is NMT 0.15%, Ondansetron impurity D is NMT 0.12 %,Any other secondary peak is NMT 0.1% and sum of all secondary peaks is NMT 0.5% (Pharmacopoeia 2018).

Stability Studies: In any rational design and evaluation of dosage forms for drugs, the stability of

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the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity. However, the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature (ICH Guideline 2003).

The tablets were packed in the Alu-Alu blister pack. Alu-Alu Blister packs were subjected to charge for the stability as per the ICH Guidelines, i.e., 1.30°C / 75 % RH (±2°C / ±5% RH), 2.40°C / 75 % RH (±2°C /±5% RH).

Alu-Alu Blister packs were subjected to charge for the stability for the period of three months. The samples were withdrawn at Initial stage, 1month and 3 months from all storage conditions.

Comparison with Marketed Formulation

The dissolution of six marketed tablets was compared with our optimized formulation and the sample analysed using cumulative percentage drug release, assay, and disintegration time.

RESULTS AND DISCUSSION

Drug-Excipient Interaction Study By Chemical Analysis

Compatibility study was done to know possible interactions between drug and excipients. The limit for related substance as per IP is NMT 0.10% for per cent highest unknown impurity and NMT 0.50% for per cent total impurity. No physical changes were observed. The impurity profile study i.e. related substance determination of drug along with excipients did not show any significant change, so the drug was compatible with the excipients (Table 4).

Table 4. Drug-Excipient Compatibility Study by impurity profile.

Drug : Excipient	Ratio	Impurity profile					
		25⁰C / 60% RH		40⁰C / 75% RH		60⁰C	
		%HI	%TI	%HI	%TI	%HI	%TI
Ondansetron + Mannitol (Perlitol SD 200)	1:1	0.018	0.061	0.042	0.070	0.015	0.025
Ondansetron + Microcrystalline Cellulose PH 102	1:1	0.021	0.041	0.017	0.031	0.024	0.056
Ondansetron + Crospovidone (Polyplasdone XL10)	1:1	0.022	0.057	0.032	0.057	0.025	0.056
Ondansetron + Sodium starch glycollate	1:1	0.026	0.034	0.022	0.046	0.025	0.052
Ondansetron + Croscarmellose sodium	1:1	0.019	0.037	0.018	0.034	0.051	0.081
Ondansetron + Magnesium stearate	1:1	0.020	0.038	0.017	0.042	0.030	0.067
Ondansetron + Colloidal silicon dioxide	1:1	0.027	0.069	0.017	0.070	0.188	0.251
Ondansetron + Sodium Saccharin	1:1	0.053	0.091	0.022	0.031	0.043	0.070
Ondansetron + Acesulfame potassium	1:1	0.041	0.078	0.027	0.057	0.051	0.091
Ondansetron + Sucralose	1:1	0.016	0.023	0.014	0.046	0.159	0.198
Ondansetron + Peppermint flavour DM 9140	1:1	0.015	0.022	0.017	0.034	0.026	0.057
Ondansetron	1:1	0.021	0.029	0.022	0.042	0.023	0.054

% Highest Unknown Impurity= %HI
% Total Impurity= %TI

Drug-Excipient Interaction by FTIR Spectroscopy

The formulation of orally disintegrating tablet of Ondansetron was evaluated for interaction studies to ensure that there is no interaction between drug and excipients. For the confirmation of interaction of drug in the formulations the FTIR spectra of excipients were taken and compared with the FTIR spectrum of pure drug. The results revealed that there were no interaction between the drug and excipients (Skoog, Holler et al. 1980) (Figures 2-3).

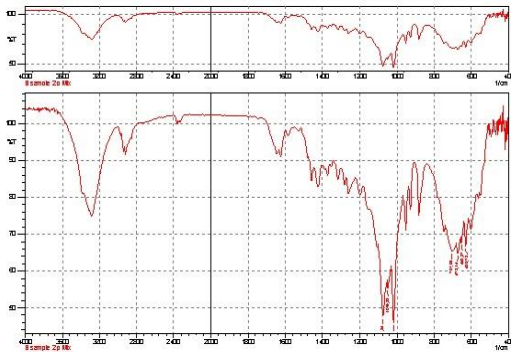

Figure 2. *FTIR spectrum of pure drug ondansetron.*

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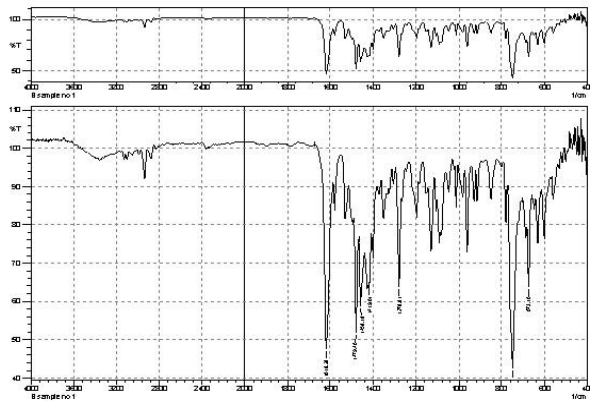

Figure 3. *FTIR spectrum of a physical mixture of ondansetron and excipients.*

The overlain FTIR spectrum of Ondansetron shown in figure number 2 and 3, which clearly indicated that peaks observed in spectrum of pure drug Ondansetron were also seen in spectrum of physical mixture of drug and excipients along with some new intense peak. Therefore, it could be concluded that all characteristic functional group of Ondansetron (i.e. O-H at 3344, N-CH3 at 2906, C=O at 1651, C-N 1064) were found in physical mixture of drug & excipients.

Evaluation Tests

Evaluation of granules: Evaluation parameters like bulk density, tapped density, Carr's compressibility index and Hausner's ratio of granules of Ondansetron layer are shown in Table 5 and 6 (Liberman and Kanig 1987). In the above results, % Carr's index for all batches found to be less than 20% and Hausner's ratio was found to be less than 1.25 which indicated good flow property.

Selection of Superdisintegrants: Approach 1

Weight variation test: All the batches of orally disintegrating tablet showed deviation below 7.5% as the allowable limit is 7.5% (Table 7).

Thickness: The thickness for all batches is depicted in table number 7. The thickness of different batches of orally disintegrating tablet was found in the range of 2.84 – 2.86 mm.

Hardness test: The results are tabulated in table number 7. Hardness of orally disintegrating tablet varied from 2 to 5 kg/cm2.

Friability: The values of friability test are given in table number 7. All the batches showed friability within the official limit i.e. less than 1%, thus all the batches passed the friability test.

"In vitro" dispersion test: "In vitro" dispersion time was measured by dropping two tablets in a 100 ml flask containing of distilled water with stirring. Then this solution passes through 710µm sieve. No particle of any formulations was retained on sieve thus all the batches passed the "in vitro" dispersion test.

Disintegration time: The most important parameter that is needed to be optimized during the development of fast disintegrating tablet is disintegration time of the tablets. The disintegration test of the tablet was conducted in purified water. The limit of disintegration for orally disintegrating tablet is NMT 30 seconds as per Indian Pharmacopoeia 2018. The batch number F7 containing superdisintegrant Crospovidone (Polyplasdone XL 10) in higher concentration shows the disintegration time below 10 seconds and having more disintegration power as compared to other superdisintegrants. Disintegration study for all batches is depicted in table number 8.

Wetting time: Wetting time for all the formulations were found in range of 12 to 21 seconds. The batch containing superdisintegrant Crospovidone (Polyplasdone XL 10) in higher concentration shows the wetting time near to 12 seconds and time required to penetrate water into tablet is minimum as compared to other superdisintegrants. Wetting time study for all batches is depicted in table number 8.

"In vitro" drug release: The "in vitro" drug release of Ondansetron was found to be in the range of 90.28% to 97.85%. As per IP standard (NLT 80% release within 10 minutes) all the batches of Ondansetron passed the "in vitro" drug release test because there was no any effect of excipient seen on "in vitro" drug release given in table number 8.

Assay: The test was performed for all the batches as per the procedure discussed in experimental part. The assay of Ondansetron in formulation is in the acceptable limit. The results of "in vitro" drug release and Assay are given in Table 8.

Selection of Superdisintegrants: Evaluation of orally disintegrating tablet of Ondansetron was done.

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Table 5. Evaluation of Granules Property of Ondansetron orally disintegrating Tablet Blend (Approach 1).

Formulations	**F1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Bulk density (gm/ml)	0.48	0.48	0.46	0.47	0.48	0.46	0.49	0.48	0.46
Tapped density (gm/ml)	0.56	0.56	0.55	0.55	0.56	0.54	0.57	0.56	0.55
% Carr's index	15.2	13.99	15.52	13.76	14.53	14.64	14.72	14.63	16.01
Hausner's ratio	1.17	1.15	1.18	1.15	1.17	1.17	1.16	1.17	1.19
LOD (%)	2.2	2.45	2.50	2.38	2.32	2.41	2.15	1.85	2.38

% Highest Unknown Impurity= %HI
% Total Impurity= %TI

Table 6. Evaluation of Granules Property of Ondansetron orally disintegrating Tablet Blend (Approach 2).

Formulations	**F_{10}**	**F_{11}**	**F_{12}**
Bulk density (gm/ml)	0.4671	0.4825	0.4928
Tapped density (gm/ml)	0.5582	0.5628	0.5769
% Carr's index	16.36	14.34	14.51
Hausner's ratio	1.18	1.16	1.17
LOD (%)	2.23	2.42	2.62

Table 7. *Evaluation of Tables Approach 1.*

Formulation	Weight variation (%)	Thickness (mm)	Hardness kg/cm²	% Friability
F1	1.85	2.85	2-3	0.27
F2	3.59	2.84	2-3	0.33
F3	0.25	2.83	3-4	0.57
F4	3.67	2.86	2-3	0.40
F5	0.33	2.85	3-4	0.31
F6	0.91	2.85	3-4	0.53
F7	2.64	2.84	2-3	0.29
F8	0.39	2.86	3-4	0.53
F9	0.59	2.84	4-5	0.67

Results shows that the weight variation (0.91 to 3.67 %), thickness (2.84 to 2.86mm), hardness (2 to 5 kg/cm2) and friability (less than 1%) limit were found to be acceptable for all the formulations. This shows that the tablets of all the formulations having good strength and sufficient hardness.

The limit for per cent drug release is NLT 80% in 10 minutes. The per cent drug release was found to be in between 90.28 to 97.85% and the assay was found to be in between 98.43 to 99.30% this shows that the all formulations of orally disintegrating tablet were having good drug release. Wetting time was found to be within the limit.

The most important evaluation parameter for orally disintegrating tablet is disintegration time; from the above result it was clear that the formulation F7 comprising concentration of Crospovidone (Polyplasdone XL10) 10 mg was having minimum disintegration time (i.e. 7 seconds) and maximum drug release thus the formulation F7 was considered for the further study. When analysed under a scanning electron icroscope, Crospovidone (Polyplasdone XL10) particles stand out porous and granular shape as compared to Croscarmellose sodium, sodium starch glycollate particles which are fibrous, nonporous structure. Crospovidone (Polyplasdone XL10) works by mechanism that it rapidly wicks saliva into the tablet which generate the volume stretching and create hydrostatic pressures obligatory to provide faster disintegration in the mouth (Figure 4).

Croscarmellose sodium, sodium starch glycollate, depends mechanically on swelling for disintegration but Crospovidone disintegrate by collection of swelling and wicking as it is having highly crosslink density (Pahwa and Gupta 2011). Increase in concentration of Crospovidone (Polyplasdone XL10) revealed decrease in disintegration time.

Selection of Sweetner: Approach 2:

Weight variation test: All the batches of orally disintegrating tablet showed deviation below 7.5% as the allowable limit is 7.5 % (Table 9).

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Table 8. *Evaluation of tablets: Approach 1.*

ID	Disintegration time (seconds)	Wetting time (seconds)	% Cumulative drug release	Assay (%)
F1	12.00	16	96.13	98.58
F2	12.00	14	92.59	99.33
F3	15.00	21	93.86	98.77
F4	12.00	19	90.28	99.05
F5	14.00	17	91.63	98.54
F6	13.00	18	94.69	98.43
F7	7.00	12	97.85	99.11
F8	10.00	13	90.78	99.32
F9	13.00	17	96.23	99.18

Thickness: The thickness for all batches is depicted in table number 8. The thickness of different batches of orally disintegrating tablet was found in the range of 2.85 – 2.86 mm (Table 9).

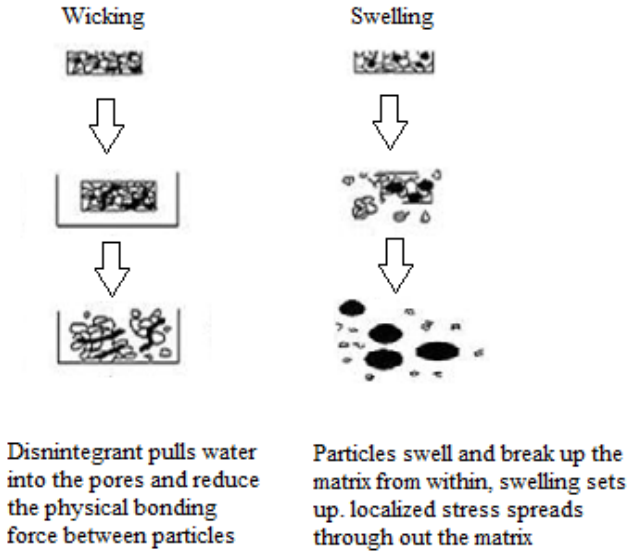

Figure 4 - Swelling and wicking mechanism of superdisintegrants (Bhowmik et al. 2014).

Table 9. *Evaluation of tablets: Approach 2.*

Form-ulation	Weight variation (%)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)
F10	2.08	2.85	2-3	0.33
F11	3.08	2.85	2-3	0.37
F12	0.52	2.86	3-4	0.49

Hardness test: The results are tabulated in table number 9. Hardness of orally disintegrating tablet varied from 2 to 4 kg/cm2.

Friability: The values of friability test are given in table number 9. All the batches showed friability within the official limit i.e. less than 1%, thus all the batches passed the friability test.

"In vitro" dispersion test: "In vitro" dispersion time was measured by dropping two tablets in a 100 ml flask containing of distilled water with stirring. Then this solution passes through 710um sieve. No particle of any formulations was retained on sieve thus all the batches passed the "in vitro" dispersion test.

Disintegration time: The most important parameter that is needed to be optimized during the development of fast disintegrating tablet is disintegration time of the tablets. The disintegration test of the tablet was conducted in purified water. The limit of disintegration for orally disintegrating tablet is NMT 30 seconds as per Indian Pharmacopoeia 2014. Disintegration study for all batches is depicted in table number 10. The disintegration time of different batches of orally disintegrating tablet was found in the range of 6.00 to 7.00 seconds. Figure 5 shows disintegration of tablets in test tube.

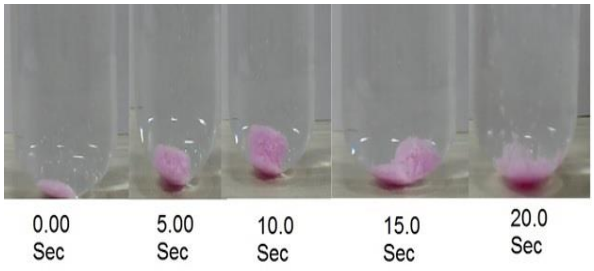

Figure 5. Disintegration of tablets in Test tube

Wetting time: Wetting time for all the formulations were found in range of 13 to 23 seconds. Wetting time for all batches is depicted in Table 10.

"In vitro" drug release: The "in vitro" drug release of Ondansetron was found to be in the range of 92.89% to 97.20%. As per IP standard (NLT 80% release within 10 minutes) all the batches of Ondansetron passed the "in vitro" drug release test. (Table 10).

Assay: The test was performed for all the batches as per the procedure discussed in experimental part. The assay of Ondansetron in formulation is in the acceptable limit. The acceptable limit for the assay of Ondansetron in formulation is 90-110% (Table 10).

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Table 10. *Evaluation of tablets: Approach 2*

IDs	Disintegration time(seconds)	Wetting time (s)	% Drug release	Assay (%)
F10	7.00	19.00	97.20	98.87
F11	6.00	13.00	95.57	97.96
F12	7.00	23.00	92.89	97.75

Table 11. Evaluation of tablets: Approach 2 (Related substances).

ID	2-Methyl imidazole	Ondansetron Impurity D	Any other secondary peak	All other secondary peak
F10	ND	0.004%	0.028%	0.052%
F11	ND	0.021%	0.099%	0.22%
F12	ND	0.10%	0.17%	0.67%

ND= not detected

Related substances: Related substances study was carried out on the batch F10, F11, F12 and from the study results it was clear that peak of 2-Methylimidazole was not detected in the formulation. Ondansetron Impurity D, any other secondary peak and all other secondary peak for the batch F10 and F11 was found within the specified limit but the formulation containing Acesulfame potassium F12 it was found out of the specification (Table 11).

Selection of Sweetener

Evaluation of orally disintegrating tablet of Ondansetron was done. Results shows that the weight variation (0.52 to 3.08 %), thickness (2.84 to 2.86mm), hardness (2 to 5 kg/cm2) and friability (less than 1%) limit were found to be acceptable for all the formulations. This shows that the tablets of all the formulations having good strength and sufficient hardness. Disintegration time was found to be in between 6.00 to 7.00 seconds which was acceptable. Wetting time was found to be within the limit. The assay of Ondansetron in formulation was found to be in between 97.96 to 98.87 which was found to be within the acceptable limit. The limit for per cent drug release is NLT 80% in 10 minutes. The per cent drug release for the formulation F10 F11 and F12 was found to be 97.20, 95.57 and 92.89 respectively which was found to be within the limit.

In the related substances study all impurity peaks of formulation F10 and F11 was found within the specified limit but in formulation F12 containing Acesulfame potassium, peaks was found out of the limit this may be due to unknown interaction of Acesulfame potassium with Ondansetron in the compressed tablet formulation. Hence from the above results F10 and F11 batches were taken for the further study (i.e. stability studies).

Stability Studies

Appearance: Tablets kept for stability studies were examined. The colour of the formulation F10 was similar before and after stability studies. Surface texture of the formulations packed in Alu-Alu Blister packs does not show any significant change at 30□C/75%RH (±20 C/±5RH) and 40□C/75%RH (±20 C/±5RH) after 1 month and 3 month. This indicated that the tablets not absorb moisture from the environment. The black spots are observed on the formulation F11 (Fig. No. 6) at 40□C/75%RH (±20 C/±5RH) after 1 month this may because of thermal decomposition of sucralose in the formulation so the formulation F10 was taken for the further stability studies.

Figure 6. *Comparative appearance for batches F10 and F11*

Drug content: Drug content was determined at every specified interval of time. The drug content was calculated by HPLC method described in IP (Table no. 12). At the end of 1 months and 3 months the drug content found in Formulation F10 was above 90% and below 110 %. This indicates that Ondansetron orally disintegrating tablets packed in Alu-Alu Blister pack was stable in presence of the excipients used, and stored at high temperature and in presence of high humidity.

Disintegration: At the end of 1 month and 3 month disintegration time found in Formulation F10 was below 10 seconds. This indicates that Ondansetron orally disintegrating tablets packed in Alu-Alu Blister pack was having no change in disintegration time in presence of theexcipients used, stored at high temperature and high humidity (Table 12).

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"In vitro" drug release: The following are the 1 month and 3 month stability samples which were analysed on HPLC to find out the "in vitro" drug release Table 12.

Table 12. *Drug content, "in vitro" disintegration time, "in vitro" drug release of the optimized batch for stability studies packed in Alu-Alu blisters.*

Time	Conditions	Drug Content (%)	DT (s)	% drug released
Initial	N/A	98.87	7.00	97.20
1 Month	30⁰ C/75%RH	96.39	7.00	98.79
	40⁰ C/75%RH	97.25	7.00	98.71
3 Month	30⁰ C/75%RH	96.35	7.00	97.84
	40⁰ C/75%RH	95.25	8.00	97.33

Related substances study: Related substances study was carried out on the optimized formulation and from the study results it was clear that 2-Methylimidazole, Ondansetron Impurity D, any other secondary peak and all other secondary peak was not detected in the formulation (Table 13).

Table 13. *"In vitro" drug release for the optimized batches use for stability studies.*

Formulation F10	**Results**
2-Methylimidazole	Not detected
Ondansetron Impurity D	0.01%
Any other secondary peak	0.03%
All other secondary peak	0.13%

Comparison with Marketed Formulations: By comparing optimized formulations with marketed formulation in the sense of disintegration, "in vitro" drug release and Assay it can be clear that the optimized formulation was found to be comparable with marketed preparation (Table 14).

Dissolution Studies

Multimedia dissolution study was carried out on the Ondansetron orally disintegrating tablets. The study was carried out on three different medium 0.1N HCl, pH4.5 Acetate buffer & pH6.8 Phosphate buffer. The sampling point for the dissolution was kept at 05, 10,15,20,30 Minutes. The dissolution was carried out as per the parameters given in IP 2018. The result of multimedia dissolution study was given in Table no. 15. (Figure no. 7). The results shows that dissolution of Ondansetron was found at lower side in pH 6.8 Phosphate buffer this may be due to Ondansetron is a weakly basic drug comprising of BCS Class-II and its solubility is depend on pH which impacts on the dissolution . Ondansetron shows high solubility at low pH and low solubility at high pH. In some studies precipitation of Ondansetron was reported in pH6.8 Phosphate buffer (Anilkumar 2016).

CONCLUSIONS

The most important evaluation parameter for orally disintegrating tablet is disintegration time. In the first approach three various Superdisintegrants i.e. sodium starch glycollate, Croscarmellose sodium and Crospovidone (Polyplasdone XL10) was taken for the study in varying concentration. Indian Pharmacopoeia specified the limit of disintegration should not be more than 30 seconds. Formulation F7 having concentration of Crospovidone (Polyplasdone XL10) 10 mg was having disintegration time below 10 seconds.

The second approach consist to selection sweeteners i.e. sodium saccharin, sucralose and Acesulfame potassium. Concentration of Acesulfame potassium in the formulation increases the impurity in the formulation, Sucralose affects the stability of the formulation hence sodium saccharin was found to be superior. It was concluded that Ondansetron was successfully formulated in orally disintegrating tablet which has shown good stability up to 3 months, faster disintegration and better drug release.

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