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DESIGN AND DEVELOPMENT OF ONDANSETRON ORALLY DISINTEGRATING TABLETS AND ITS OPTIMIZATION USING DESIGN OF EXPERIMENT

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ABSTRACT

Ondansetron is the first of a new class of drugs, selective serotonin receptor antagonist (5 hydroxy tryptamine type 3) used as an anti emetic associated with cancer chemotherapy. Its Orally Disintegrating Tablet has been developed for patients who find swallowing difficult by freeze dried technology by RP Scherer Corporation and Scherer DDS. The aim of this study was to design a new orally disintegrating tablet that has high hardness and a fast disintegration rate using conventional tablet technology. Ondansetron ODT was prepared by using traditional technology like direct compression and wet granulation technique. As blend exhibited poor flow in direct compression process, so wet granulation process was finalized. Bitter taste of Ondansetron has been masked by use of sweetener like aspartame and peppermint flavor. Quick disintegration has been achieved by use of surfactant in the granulating solvent and superdisintegrant like crospovidone in both intra and extragranular part. Design space has been created by use of different concentrations of both binders as well as disintegrant with the help of DOE and a robust formulation has been made. In vitro release profile of both formulations prepared by freeze drying and wet granulation is matching. Formulation prepared by wet granulation process has been found acceptable to volunteers in term of taste, mouth feel and convenience of administration.

INTRODUCTION: Ondansetron is the first of a new class of drugs, selective serotonin receptor blocker (5 hydroxy tryptamine type 3) used as anti emetic associated with cancer chemotherapy [1-3]. ODT has been developed for patients who find swallowing difficult; it disintegrates quickly on the tongue and is swallowed with saliva.

Ondansetron ODT is better dosage form in term of ease of administration than conventional Ondansetron tablet and is also equally effective in controlling the emesis induced by anticancer agent [4]. An Ondansetron ODT has been developed by using wet granulation technique and optimized using design of experiment.

An Ondansetron Orally Disintegrating Tablet (Zofran ODT®) has been developed by RP Scherer Corporation and Scherer DDS (Swindon, United Kingdom) and is marketed by Glaxo Smithkline and its photograph is shown in **Figure 1**.

Zofran ODT® tablets are freeze-dried, strawberry flavored orally administered formulation of Ondansetron which rapidly dissolves on tongue and does not require water to aid dissolution or swallowing.

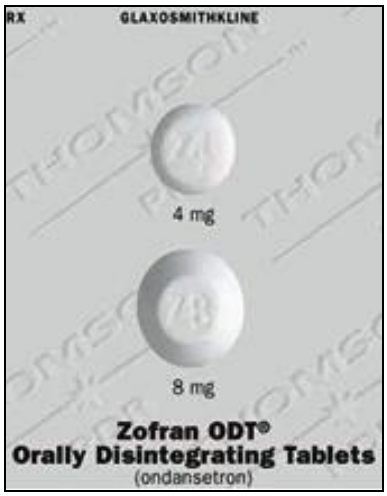

FIGURE 1: PHOTOGRAPH OF MARKETED PRODUCT

Its disintegration time is around 2-3 seconds when tested using United State Pharmacopeia (USP)/European Pharmacopeia (EP) test method. Zofran ODT® is manufactured by patented lyophilized Zydis® technology.

Freeze-Drying or Lyophilization: Freeze drying is the process in which drug solution or suspension is freezed and solvent is removed by sublimation. This technique creates an amorphous highly porous structure which aid in rapid dissolution or disintegration of the tablet dosage form.

Disadvantage of Lyophilization or Freeze Drying:

a) Generally Lyophilization is very expensive and time consuming process.

b) Generally Lyophilized formulations have low hardness and high friability. For this reason, conventional packing like HDPE bottles cannot be used for the lyophilized tablets.

Objective of the current research is to develop an Ondansetron Orally disintegrating Tablets using conventional tablet technology that produces tablets of good hardness, low friability and disintegration time less than 6 seconds when tested using USP/EP Disintegration apparatus. This will serve the three purposes

i) By achieving disintegration time less than 6 seconds, the ODT will be equivalent to freeze dried tablets in term of mouth feel, and ultimately patient compliance.

ii) By achieving good hardness and friability (less than 1%), these tablets can be packed in traditional bottle packs and can be transported without damaging the tablets. It does not require special handling by patients and can be taken very conveniently.

iii) It will also comply to the Pharmacopoeial requirement with respect to disintegration time (less than 10 seconds).

To achieve the above objective, design of experiment was applied to optimize the concentration of critical excipients like binder and disintegrants. Design space was created that shows which combination of disintegrant and binder concentration can produce ODT with disintegration time less than 6 seconds. This resulted in robust formulation with desired product characteristics.

MATERIALS AND METHODS:

Materials: Following active ingredient and excipients were selected for the formulation of ODT. Details are tabulated in the **Table 1.**

TABLE 1: ACTIVE INGREDIENT AND EXCIPIENTS SELECTED FOR THE FORMULATION OF ODT

Category	Ingredients	Manufacturer's Name
Active Ingredient	Ondansetron Base	Dr. Reddy's Labs
Diluent	Mannitol,	Roquette
Diluent	Microcrystalline cellulose	FMC Corporation
Diluent	Silicified MCC (Prosolve)	JRS Pharma
Disintegrant	Crospovidone	BASF
Binder	Pregelatinized starch	Colorcon
Sweetener	Aspartame	Nutra Sweet
Flavor	Peppermint	Givaudan
Surfactant	Sodium Lauryl Sulphate	Cognis
Glidant	Colloidal Silicon Dioxide	Evonik Degussa Corporation
Lubricant	Magnesium stearate	Ferro Corporation

All other reagents and chemicals of analytical grade were used in our experiments.

Methods:

Manufacturing of Orally Disintegrating Tablets: Ondansetron Orally Disintegrating Tablets were

manufactured by both direct compression and wet granulation. In case of direct compression, blend exhibited the poor flow so wet granulation process was selected for all further trials.

In Wet granulation, ingredients like Ondansetron base, Mannitol, Microcrystalline Cellulose, Silicified MCC, Crospovidone, PG starch were taken in a Rapid Mixer Granulator and granulated using hydro alcoholic or aqueous solution of Sodium Lauryl Sulphate. The wet mass was dried in a rapid dryer and after milling; sized granules were mixed with other extragranular ingredients and compressed at an average weight of 100 mg for 8 mg strength and at 50 mg average weight for 4 mg strength using suitable punches.

Tablets with different concentration of Sweeteners and flavors were prepared and evaluated as per **Table 2a and 2b**. Tablets with different ratio of disintegrant (both intragranular and extragranular) were prepared as per **Table 3**.

Tablets with different ratio of binder and disintegrant as per two-level design (2^2 factorial design) were prepared as per **Table 4**.

Evaluation of Ondansetron Orally Disintegrating Tablets:

1. **Tablet Hardness Test:** Tablets must be hard enough to withstand mechanical stress during packaging, shipment and handling by consumer. The tablet hardness[5] is the force required to break the tablet into halves and was measured by using Venkel Hardness tester (VK 200). Tablet is placed properly between the measuring jaw against the sensing jaw. After pressing the Test button, power jaw begin to move towards the tablet and pressed against the sensing jaw. When tablet fracture, the moving jaw stop and hardness value is displayed on red LED of front panel. Tablet hardness is measured in newton or Kg/cm^2 or KP.

2. **Friability:** Friability test[5] is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Electrolab friabilator was used for the Purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a transparent chamber made of synthetic polymer with polished internal surface that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Preweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed core tablets should not lose more than 1% of their weight.

3. **Disintegration Time:** The disintegration time[5] of tablet was measured in water (37 ± 2^oC) by Electrolab disintegration apparatus complying as per EP/USP pharmacopoeia.

4. **Fineness of dispersion:** One Tablet is dispersed in 50 ml water and should pass through sieve # 22.

5. ***In-Vitro* Release Profile of Formulated Tablets:** Dissolution profile is very important for any Orally disintegrating Tablets, so that it matches in its efficacy with the innovator. Dissolution profile was done in USP recommended medium that is 0.1 N HCl, 500 ml media volume, USP Type II apparatus and 50 rpm. The sample of 10 ml was withdrawn at 5, 10 and 15 min and its absorbance was measured at 309 nm.

6. **Analysis of Variance:** ANOVA for factor influence study was applied to results obtained with different concentration of binder and disintegrant as per Table 4 by using Design Expert® software Version 8.0.4.1 (Statease Inc., Minnepolis).

RESULTS AND DISCUSSION:

Optimization of Critical Excipients:

Optimization of Sweetener and Flavor: Ondansetron is slightly bitter in taste. Aspartame[6] and Peppermint Flavor were selected for taste masking and improving palatability of the product. Formulations with different concentrations of both aspartame and flavor were prepared and given to volunteers. Based on the taste panel outcome, following concentration of sweetener and flavor were finalized;

Sweetener: 3.7% and Flavor: 0.9%

Palatability was found to be very good with 3.9% and 4.1% of sweetener, so 3.9% of sweetener was finalized.

TABLE 2A: OPTIMIZATION OF SWEETENER

Ingredients	Formulations				
	F1	F2	F3	F4	F5
Sweetener (%w/w)	3.3	3.5	3.7	3.9	4.1
Flavor (%w/w)	1.0	1.0	1.0	1.0	1.0
Palatability	Bitterness Exist	Bitterness Exist	Good	Very Good	Very Good

TABLE 2B: OPTIMIZATION OF FLAVOR

Ingredients	Formulations			
	F6	F7	F8	F9
Sweetener (%w/w)	3.9	3.9	3.9	3.9
Flavor (%w/w)	0.8	0.9	1.0	1.1
Palatability	Good	Good	Good	Good

Palatability was good in all experiments (F6 to F9) with different concentration of flavor, so 0.9% of flavor was finalized.

The formulation at this concentration was acceptable to most of the volunteers. These concentrations were fixed in all further formulation trials

Optimization of Granulation Solvent: Tablets manufactured by both aqueous and hydro alcoholic solution of sodium lauryl sulphate were evaluated for all parameters like disintegration time and it was observed that tablets prepared with aqueous granulation require little more compression force to compress the tablets at the desired hardness level and also its disintegration time was more than the tablets prepared using hydro alcoholic solution. This may be because of hard nature of granules prepared by aqueous granulation which take more force to compress into tablets.

Generally, hard granules also take time to get proper wetting and disintegrate. The granules prepared by hydro alcoholic solution appear to be less hard and required comparatively less compression force to compress into tablets and also disintegrate faster when compared to tablets prepared by aqueous granulation. So granulation with hydro alcoholic solution was finalized.

Optimization of Binder and Disintegrant: For any Orally disintegrating tablets, concentration of binder and disintegrant is critical as binder is required to achieve the desired hardness of tablets so that formulation is less friable and easy to transport without damaging the tablets and easy handling by patients. Disintegrant is critical for quick disintegration of tablet and ultimately better mouth feel and compliance by the patients.

Comparison of Tablets prepared by disintegrant addition (Only extragranular and combination of intragranular and extragranular): Different ratio of disintegrant (both extragranular and intragranular) as per Table 3 were used to manufacture Tablets.

TABLE 3: DIFFERENT RATIO OF DISINTEGRANT (BOTH EXTRAGRANULAR AND INTRAGRANULAR)

Experiment No	Disintegrant Intragranular (%)	Disintegrant Extragranular (%)	Disintegration Time (sec.)
1	0	100	7
2	100	0	6
3	50	50	6
4	30	70	5
5	70	30	6

There was no difference in disintegration time of tablets when 100% of disintegrant was used intragranular and extragranular. There was slight reduction in disintegration time when 50% disintegrant was added in both intragranular and extragranular part.

Tablets prepared with combination of both intra (30%) and extragranular disintegrant (70%) show less disintegration time. So 30% of total disintegrant in the intragranular part and 70% disintegrant in the extragranular part was finalized.

Optimization of Binder and Disintegrant by Design of Experiment: To optimize the ratio of binder and disintegrant, two level design (2^2 factorial design) with three center points was applied. It has two factors, each at two levels. These are referred to as low and high levels and are numerically expressed as -1 and +1.

Three experiments were conducted by keeping level of both the binder and disintegrant at intermediate level (numerically expressed as 0, 0) and is referred as three center points.

Keeping hardness and friability (less than 1%) fixed for all these experiments, disintegration time was considered as the response factor: Design layout of these experiments is tabulated in **Table 4**.

TABLE 4: DESIGN LAYOUT

Std	Run	Factor 1	Factor 2	Response 1
		A: Disintegrant (%)	B: Binder (%)	Disintegration time (Seconds)
3	1	6	6	7
2	2	14	2	4
7	3	10	4	5
4	4	14	6	6
5	5	10	4	6
1	6	6	2	5
6	7	10	4	5

Concentration of binder and Disintegrant at Intermediate (0) level were 4% and 10% respectively. Concentration of binder and Disintegrant at high (+1) level were 6% and 14% respectively. Concentration of binder and Disintegrant at low (-1) level were 2% and 6% respectively.

Data Analysis:

Effect analysis: Effect analysis of above experiments and their response factors using Design Expert® is tabulated in **Table 5**.

TABLE 5:

	Term	Effect	Sum Square	% Contribution
Require	Intercept	-	-	-
Model	A-Disintegrant	-1	1	17.5
Model	B-Binder	2	4	70
Error	AB	0	0	0
Model	Curvature	-0.09	0.05	0.83
Error	Lack of Fit		0.00	0.00
Error	Pure Error		0.67	11.67

Effect analysis: **Figure 2** shows the two factors are significantly controlling the disintegration time, with 70% contribution through binder (represented by point B) and 17.5 % contribution through disintegrant (represented by point A). Half-Normal plot ratifies the significant influence of the two factors on the response.

Results of ANOVA analysis using Design Expert® is tabulated in **Table 6**. ANOVA analysis reveals that Linear Model was significant (p=0.0156) with good regression parameters (R^2: 0.8750 & Pred R2: 0.8067). Lack of fit was also observed to be insignificant. Effect analysis graphically depict that disintegration time tends to increase with binder amount, however, it decreases with increase in the disintegrant amount. **Figure 3** shows 3 D picture of effect of binder and disintegrant on disintegration time.

3-D surface graphs as per **figures 3 and 4** reveal that the Binder amount has relatively higher impact on response than disintegrant amount.

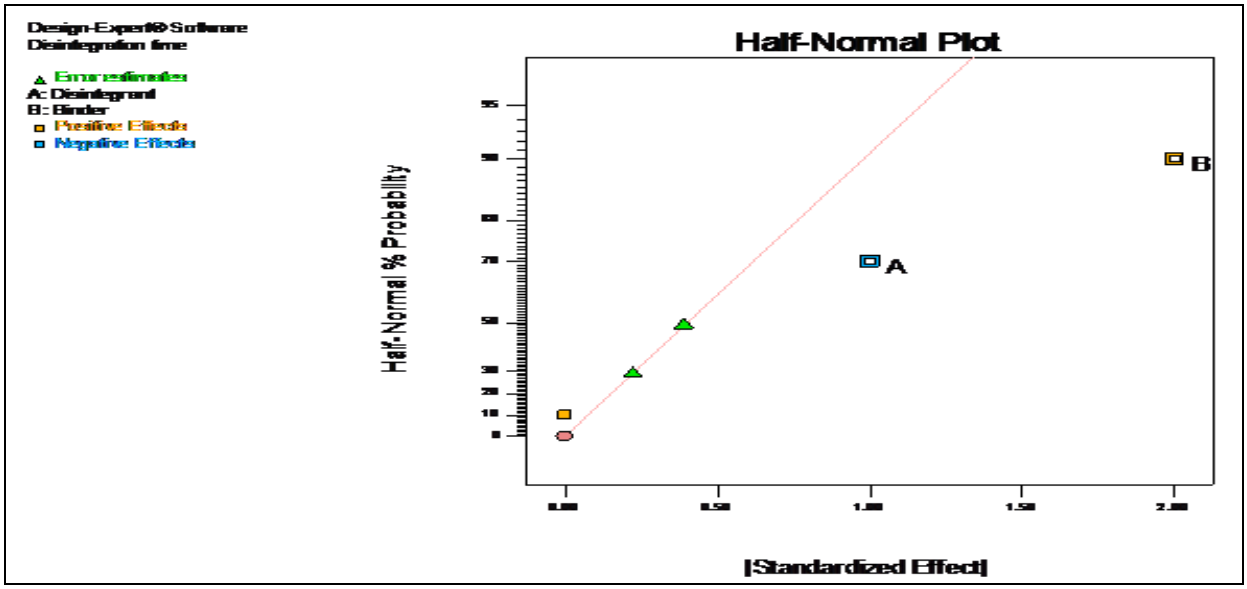

FIGURE 2:

TABLE 6:

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	5	2	2.5	14	0.0156	significant
A-Disintegrant	1	1	1	5.6	0.0771	
B-Binder	4	1	4	22.4	0.0091	
Residual	0.71	4	0.18			
Lack of Fit	0.05	2	0.02	0.0714	0.9333	not significant
Pure Error	0.67	2	0.33			
Cor Total	5.71	6				

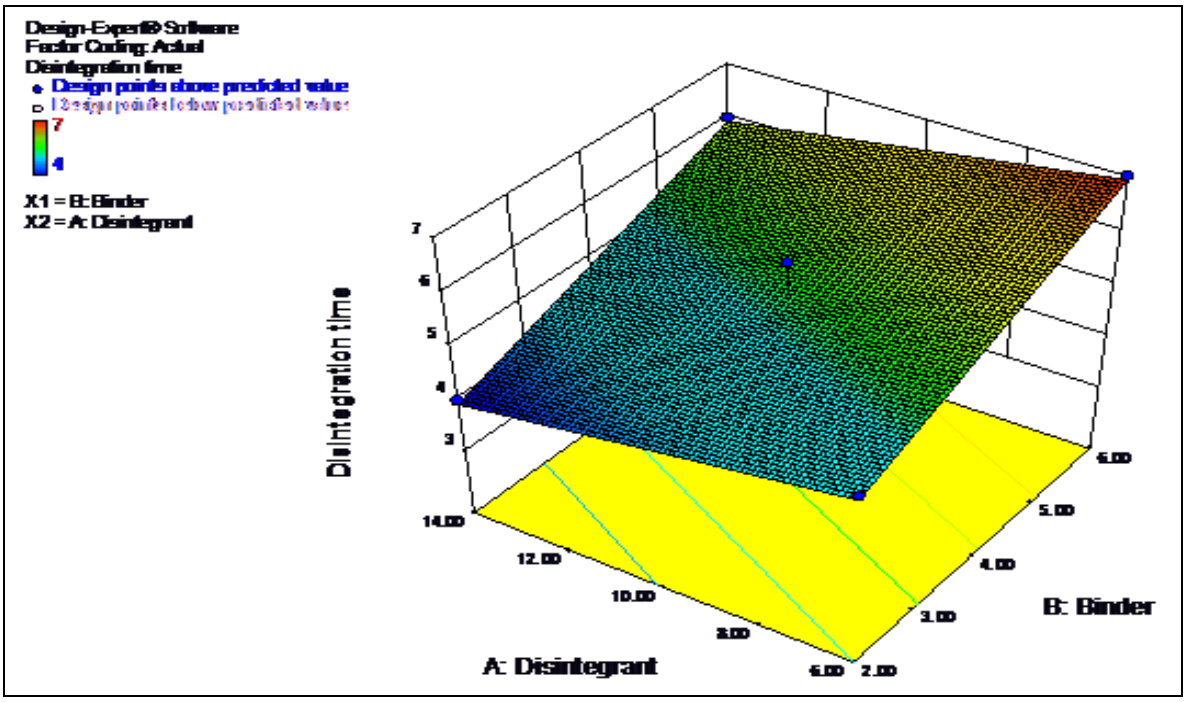

FIGURE 3

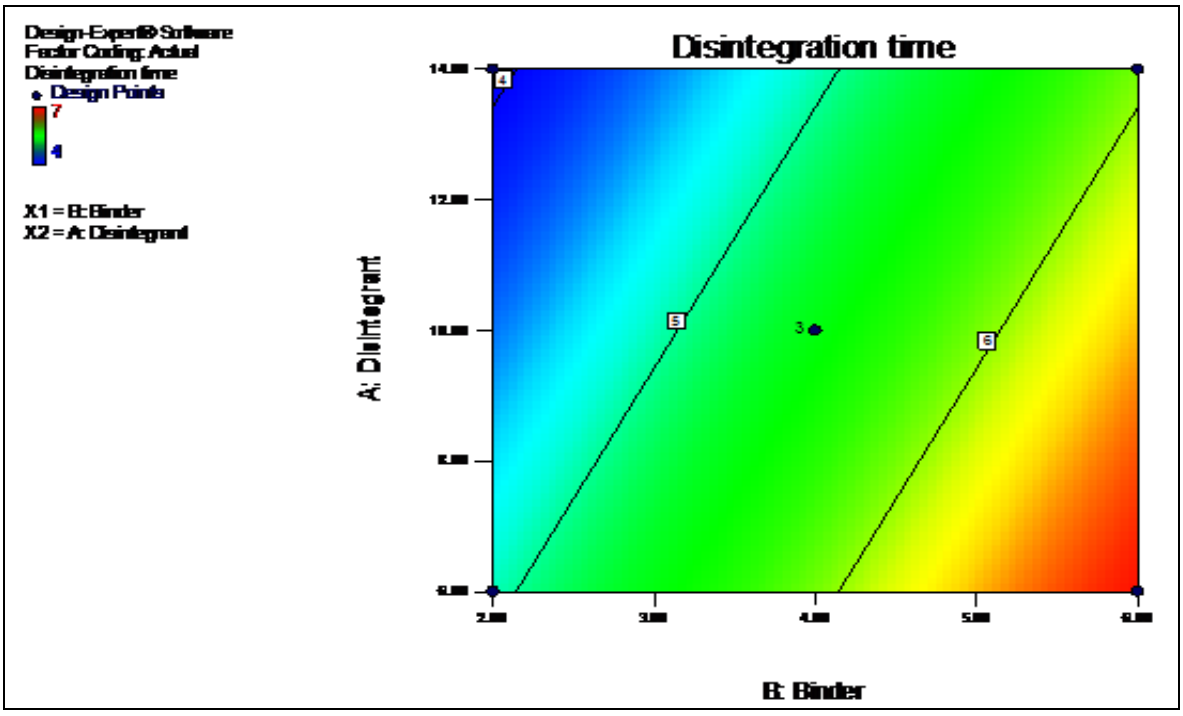

FIGURE 4

Optimization of Disintegration Time: Lower and upper limit of both Disintegrant and Binder and desired range of disintegration time is tabulated in **Table 7**.

Overlay plot as per **figure 5** shows that yellow region (lower part of plot) is the region with disintegration time less than 6 sec. This is the design space created for this formulation.

TABLE 7: DISINTEGRATION TIME

Criteria for optimization			
Name	**Goal**	**Limit (Lower)**	**Limit (Upper)**
A:Disintegrant	is in range	6	14
B:Binder	is in range	2	6
Disintegration time	is in range	0	6

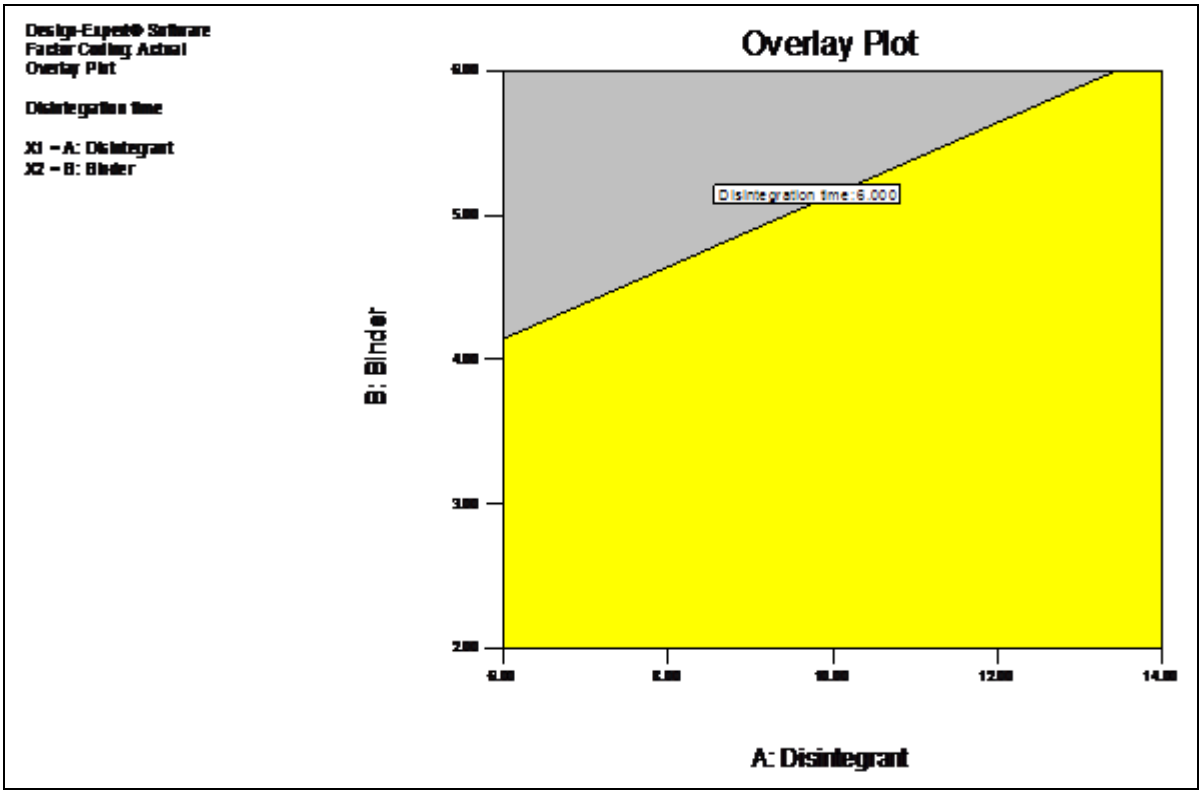

FIGURE 5

Based on earlier taste panel results on vounteers, we have already finalized the concentation of sweetener and flavor that is 3.9% and 0.9% respectively.

So following optimized composition of Ondansetron Orally disintegrating tablets as per **Table 8** has been finalized.

TABLE 8: OPTIMIZED COMPOSITION OF ONDANSETRON ODTs

Excipient	Concentration
Disintegrant	10%
Binder	4%
Sweetener	3.9%
Flavor	0.9%

Ratio of excipients in both Ondansetron Orally Disintegrating Tablets strengths (that is 4 and 8 mg) were similar and compressed using rotary compression machine and product characteristics of both the strengths is given in the **Table 9**.

TABLE 9:

Characteristic	4 mg	8 mg
Tablet weight	50 mg	100 mg
Hardness	1 – 3 kP	2 - 4 kP
Friability	NMT 1.0 %	NMT 1.0 %
Disintegration time	4-5 sec	4-5 sec
Dissolution	NLT 80% release in 10 min	

All the tablets passed the Fineness of dispersion test.

Dissolution profile of both Zofran ODT and Ondansetron ODT: Dissolution profile of both Zofran ODT (4 & 8 mg) and Ondansetron ODT (4 & 8 mg) was done and results of 8 mg are tabulated below in the **Table 10** and results of 4 mg are tabulated in **Table 11**.

TABLE 10:

Time (min)	Zofran ODT 8 mg (Cumulative %age Dissolution)	Ondansetron ODT 8mg (Cumulative %age Dissolution)
0	0	0
5	100	95
10	101	97
15	100	98

TABLE 11:

Time(min)	Zofran ODT 4 mg (%age Dissolution)	Ondansetron 4 mg (%age Dissolution)
0	0	0
5	100	98
10	100	99
15	100	99

Figure 6 shows comparative dissolution of both Zofran ODT (8 mg) and Ondansetron 8 mg ODT.

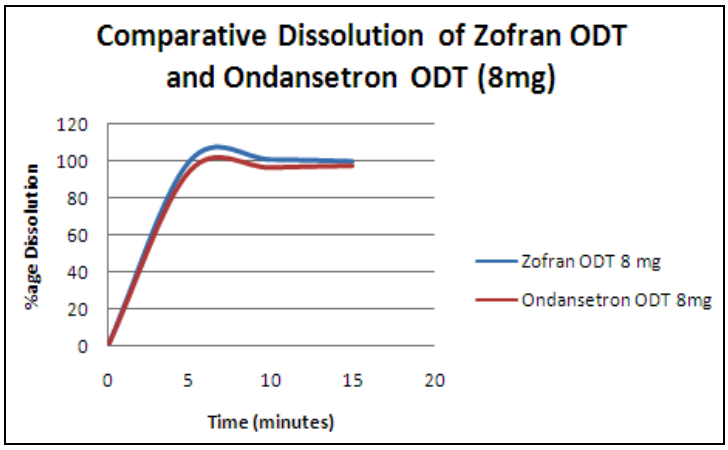

FIGURE 6: COMPARATIVE DISSLOLUTION OF ZOFRAN ODT AND ONDANSETRON ODT (8 mg)

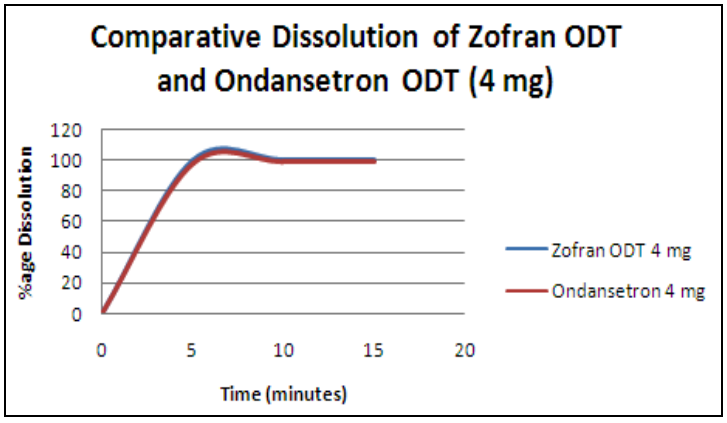

FIGURE 7: COMPARATIVE DISSLOLUTION OF ZOFRAN ODT AND ONDANSETRON ODT (4 mg)

Figure 7 shows comparative dissolution of both Zofran ODT (4 mg) and Ondansetron 4 mg ODT. Dissolution of both Zofran ODT and Ondansetron ODT are similar. There is no need to compare F2 (Similarity Factor) as per the guideline [7], as both the formulation releases more than 85% of drugs in 5 minute time point

Stability Studies: The above formulation was packed in HDPE bottles with Silica gel and charged for stability[8] at $40^{o}C$ ± 75%RH and evaluated for description, hardness, friability, disintegration time, drug content and dissolution for 3 months. The formulation was found to be stable at accelerated condition for three months.

CONCLUSION: We demonstrated that Ondansetron Orally disintegrating Tablets have been prepared by conventional tablet technology which is similar in quality attribute to the lyophilized formulation and also overcome disadvantage associated with lyophilized technology.

It was concluded that fomulation of Ondnsetron Orally disintegrating can be prepared successfully with the desired charateristics like good hardness, low friability, good dissolution and good stability with wet granulation process by carefully optimizing the critical excipients. This method to prepare ODT is simple and does not require special equipment, this technology is expected to provide better ODTs for many kind of drugs that can provide quality product to patients at an affordable price.

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