



## DEVELOPMENT AND CHARACTERIZATION OF COMPRESSED ODT FORMULATION OF INSOLUBLE LOW BITTER DRUG

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### ABSTRACT

The purpose of this investigation was to develop oral disintegrating tablets (ODT) of insoluble and low bitter drugs like zaleplon using taste enhancers as a taste masking agents. ODT of zaleplon were prepared using different superdisintegrants by direct compression method. Mannitol was used as a diluent and sodium lauryl sulphate was used as a wetting (surfactant) agent. Aspartame and Acesulfame Potassium were used for unpleasant taste masked from the zaleplon by cosifting and serial of blending with other excipients. The mixed final blend was then compressed into tablets. The formulations were evaluated for weight variation, hardness, friability, wetting time, disintegrating time, dissolution, taste evolution study and in vitro dissolution. All the formulation showed low weight variation with different disintegration time and rapid in vitro dissolution. The results revealed that the tablets containing taste enhancers had a good palatability for the patients. The drug content of all the formulations was within the acceptable limits of the United States Pharmacopoeia XXVII. The optimized formulation showed good taste masking, less disintegration time (<30seconds) and release profile with maximum drug being released at all time intervals. It was concluded that ODT's with improved zaleplon taste masking and dissolution could be prepared by direct compression containing suitable taste enhancing agent. This work helped in understanding the effect of formulation processing variables especially the disintegrating and taste enhancing agent on the drug taste masking, disintegration time and release profile. The present study demonstrated potentials for rapid disintegration in oral cavity with out water, improved taste masking and patient compliance.

**Keywords:** Oral disintegrating tablets (ODTs), Direct compression, Zaleplon, Taste enhancers, Superdisintegrant, Diluent

### INTRODUCTION

The Center for Drug Evaluation and Research defines ODT as a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed under the tongue. ODT delayed release is a solid dosage form containing medicinal substances which disintegrates rapidly, usually within matter of seconds, when place upon the tongue, but which releases a drug (or drugs) at a time other than promptly after administration<sup>1,2</sup>. The European Pharmacopoeia however defines a similar term, orodispersible tablets, or tablets intended to be placed in the mouth where it disperses rapidly before swallowing<sup>3</sup>. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down in to the stomach. In such cases, bioavailability of drug is significantly grater than those observed from conventional tablet dosage form. ODTs are appreciated by a significant segment of population, particularly children and elderly, which have difficulty in swallowing conventional tablets or capsules<sup>4,5,6</sup>.

The fundamental principle used in the development of the ODTs is to maximize its pore structure. Researchers have evaluated spray dried materials and soluble materials for development of such tablets. ODTs are prepared by various techniques, mainly direct compression, lyophilization and moulding. The simplicity and cost effectiveness of the direct compression process have positioned this techniques as an attractive alternate to traditional granulation technologies. Usually superdisintegrants are added to a drug formulation to facilitate the break-up or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants<sup>7</sup>. The problem of patient compliance in the administration of oral anti hypnotic drugs can be overcome by development of an appropriate dosage form. ODTs are best suited and have gained popularity in the recent years in oral drug therapy.

Zaleplon is widely used short-term treatment of insomnia. Chemically it is N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide. Its empirical formula is C<sub>17</sub>H<sub>15</sub>N<sub>5</sub>O, and its molecular weight is 305.34. Zaleplon is rapidly and almost completely absorbed following oral administration. Peak plasma concentrations are attained within approximately 1 hour after oral administration. Although zaleplon is well absorbed, its absolute bioavailability is approximately 30% because it undergoes

significant presystemic metabolism<sup>8</sup>. The present investigation is concerned with the development ODT of zaleplon and to investigate the effect of taste masking on the patient compliance and super disintegrating agent on the disintegration and release profile of the drug in the tablets.

### EXPERIMENTAL

#### Materials

Zaleplon API, Colloidal Silicon Dioxide NF (Aerosol 200), Mannitol NF (Pearlitol SD200), Crospovidone NF (Polyplasdone XL 10), Peppermint Flavor Premium 501500 TP0504, Acesulfame Potassium NF, Aspartame NF, Sodium lauryl sulphate and Sodium Stearyl Fumarate NF (Pruv) were obtained as gift sample from Orchid Healthcare, Irungattikottai, Chennai. All other chemicals and reagent were of analytical grade.

#### Methods

##### Formulation ODT of zaleplon

The Oral disintegrating tablets of zaleplon were prepared using the crospovidone (polyplasdone XL 10) as super disintegrates, mannitol as a diluent, aspartame and acesulfame potassium as a sweetening agents or taste enhancers, peppermint flavor as a flavor enhancers, sodium lauryl sulphate as a solubility enhancer of the drug, colloidal silicon dioxide and sodium stearyl fumarate (Pruv) as a flow promoter. The composition of the each batch was shown in table 1.

Initially development started with wet granulation process since zaleplon is a low dose molecule (maximum dose is 10mg). Commonly low strength dosage forms dose content uniformity problem and to avoid this, selected wet granulation process. The raw materials were passed through a #40mesh screen prior to mixing. The Sodium lauryl sulphate and binder (hypromellose 3cps (2%w/w)) dissolved in purified water, and used as a granulating fluid. Zaleplon, colloidal silicon dioxide, crospovidone (part 1) and mannitol were mixed together, and sufficient quantity of granulating solution was added in to dry mix and granulates to form a granulated wet mass. The wet mass was dried and passed through sieve no. 30. The dried granules were blend with crospovidone (part 2), peppermint flavor, acesulfame potassium and aspartame in

octagonal blender for sufficient time and finally lubricated with sodium stearyl fumarate (F1 & F2). The final blend was then

compressed into tablets using flat face round 9.0mm tooling on a 16 station tablet machine and tablets were evaluated.

**Table 1: Composition of different batches of oral disintegrating tablets of zaleplon for Physical and chemical characterization.**

Ingredients	F1	F2	F3	F4	F5	F6	F11
Zaleplon	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Colloidal Silicon Dioxide (Aerosol 200)	8.3	8.3	8.3	8.3	8.3	8.3	8.3
Mannitol NF (Pearlitol SD200)	139.4	142.4	153.4	149.4	145.4	141.4	140.4
Crospovidone NF (Polyplasdone XL 10)	16.0	16.0	8.0	12.0	16.0	20.0	16.0
Hypromellose 3cps	6.0	6.0	-	-	-	-	-
Peppermint Flavor Premium 501500 TP0504	2.0	2.0	2.0	2.0	2.0	2.0	3.8
Acesulfame Potassium	5.4	5.4	5.4	5.4	5.4	5.4	7.0
Aspartame	2.4	2.4	2.4	2.4	2.4	2.4	4.0
Sodium lauryl sulphate (Stephanol WA 100)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium Stearyl Fumarate (Pruv)	10.0	10.0	10.0	10.0	10.0	10.0	10.0
<b>Total</b>	<b>200.0</b>	<b>200.0</b>	<b>200.0</b>	<b>200.0</b>	<b>200.0</b>	<b>200.0</b>	<b>200.0</b>

Note: Where water was used for granulation for F1 and F2

Later direct compression process were selected, because porous nature is more in direct compression blend than wet granulation blend, so it will give faster disintegration. In this process, mannitol and colloidal silicon dioxide were together passed through sieve no. 40 (Blend 1). Zaleplon, peppermint flavor, crospovidone, aspartame, acesulfame potassium and sodium lauryl sulphate were mixed and sift together through sieve no. 60 (Blend 2). The mannitol blend (Blend 1) part and zaleplon blend (Blend 2) part were mixed with serial blending and finally passed through sieve no. 40 (F3 to F11). This final blend was compressed into tablets using flat face round 9.0mm tooling on a 16 station tablet machine and tablets were evaluated.

#### Evaluation of formulated tablets

##### Hardness

The crushing strength of the tablets was measured using an Erweka hardness tester. Twenty tablets from each formulation batch were tested randomly and the average reading noted.

##### Weight variation

Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than  $\pm 5\%$

##### Thickness

The thickness of the tablets was measured using Vernier Caliper (Mitu-tyo). Twenty tablets from each formulation batch were tested randomly and the average reading noted.

##### Friability

6.5g equivalent weight tablets were weighed and placed in a friabilator (Electrolab ET-2). Pre-weighed tablets were rotated at 25 rpm for 100 rotations. The tablets were then dedusted and re-weighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured as per the formula.

##### Disintegrating time

In vitro disintegration time was measured by using disintegration tester (Electrolab ED-2L) and tablet dropping in a 1000ml beaker containing 900ml of purified water which maintained at  $37 \pm 0.5^\circ\text{C}$ .

##### Dispersion time

In vitro dispersion time was measured by dropping a tablet in a 10 ml measuring cylinder containing 6 ml of buffer solution simulating saliva fluid (pH 6.8)

##### Wetting time

A piece of tissue paper folded twice was placed in a Petri dish (Internal Diameter = 9cm) containing 9ml of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Five tablets from each formulation were randomly selected and the average wetting time was noted.

##### Dissolution

In-vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) at 75rpm. Deionized water, 900ml was used as dissolution medium which maintained at  $37 \pm 0.5^\circ\text{C}$ . 10ml dissolution medium was withdrawn at specific time intervals. The amount of drug dissolved was determined by HPLC [Photodiode array detector (Waters 996)] by measuring the sample.

##### Taste evaluation study

The objective of this study is to conduct and evaluate the Palatability of different formulations of zaleplon oral disintegrating tablets. Zaleplon ODT was a new development; reference product is not available in market for this product for comparison of the taste evaluation. Total eight formulations were selected for taste evaluation study, six test formulations, one positive control (Placebo for zaleplon) and one is negative control (Placebo for Taste enhancers like aspartame and acesulfame potassium and

peppermint flavor). All formulations (formulation code) were randomized. Each randomization order was assigned with sequence code. For this study were selected ten healthy human male volunteers, and were assigned volunteer code.

All the ten volunteers were evaluated all eight formulations as per the randomization order. Each of the eight formulations were transferred to HDPE bottles and labeled only with formulation code. Palatability evaluation feedback format prepared and submitted to each individual volunteer and were provided with instructions

before starting study. One tablet of each formulation was given to volunteer for palatability study evaluation. The time interval between evaluations of each test formulation in the same volunteer was 30min, at after evaluated each formulation, one half of a bread slice was given to each volunteer followed by half glass of water and coca powder for neutralizing the taste buds. After completion of the study, data was compiled and evaluated the formulations and allotted the rank for all formulation, based on the average value of the each formulation.

**Table 2: Composition of different batches of oral disintegrating tablets of zaleplon for taste evaluation study**

Ingredients	F5	F7	F8	F9	F10	F11
Zaleplon	10.0	10.0	10.0	10.0	10.0	10.0
Colloidal Silicon Dioxide (Aerosol 200)	8.3	8.3	8.3	8.3	8.3	8.3
Mannitol NF (Pearlitol SD200)	139.4	142.4	153.4	149.4	145.4	141.4
Crospovidone NF	16.0	16.0	16.0	16.0	16.0	16.0
Hypromellose 3cps	-	-	-	-	-	-
Peppermint Flavor Premium 501500 TP0504	2.0	3.8	5.4	3.8	3.8	3.8
Acesulfame	5.4	5.4	5.4	6.8	4.0	7.0
Potassium Aspartame	2.4	2.4	2.4	2.4	3.0	4.0
Sodium lauryl sulphate						
(Stephanol WA 100)	0.5	0.5	0.5	0.5	0.5	0.5
Sodium Stearyl Fumarate (Pruv)	10.0	10.0	10.0	10.0	10.0	10.0
<b>Total</b>	<b>200.0</b>	<b>200.0</b>	<b>200.0</b>	<b>200.0</b>	<b>200.0</b>	<b>200.0</b>

## RESULTS AND DISCUSSION

Water insoluble diluents such as microcrystalline cellulose and dicalcium phosphate were omitted from the study as they are expected to cause an unacceptable feeling of grittiness in the mouth. Among the soluble diluents considered its advantages in terms of easy availability and negative heat of dissolution. Table 3 shows that all the formulated tablets exhibited low weight variation. In wet granulation process, addition of hypromellose at different concentrations as a binder had no pronounced effect on flow and increased disintegration time of the tablets (F1 & F2). The wetting time and *in vitro* dispersion time of the tablets were also considerably increased in tablets containing hypromellose, because less porous nature of the blend (Table 2). The drug content of all the formulations was found to be between 99.6 – 101.2% which was within the acceptable limits as per USP XXVII. The batches F3, F4, F5 and F6 were prepared using polyplasdone XL 10 at different concentrations to study its effect on disintegration time. The disintegration time depended on the amount of polyplasdone XL 10 present in tablets (4%, 6%, 8% and 10%). Batch F5, containing 8% polyplasdone XL 10, showed the least disintegration time. The

results shown in Table 3 indicate that concentration dependent disintegration was observed in batches prepared using polyplasdone XL 10 as a disintegrating agent is responsible for faster water uptake; hence it facilitates wicking action and bringing about faster disintegration. It is worthwhile to note that as the concentration of polyplasdone XL 10 increased up to 8%, the wetting also increased and disintegrating time was decreased.

Tablets with wet granulation having lower friability (<0.2%) may not break during handling on machines and/or shipping (F1 & F2). The use of a binder (hypromellose) resulted in decreased friability and less porability due to decreased porosity (Table 3). The disintegration time was found to be more than 30seconds (USP limits for ODT is NMT 30 seconds) which made us try direct compression approach

Tablets with direct compression were shown faster disintegration and more porability due to increased porosity. Batch no. F5 and F11 were shown faster disintegration and dissolution than other batches like F3, F4 and F6, because 8% polyplasdone XL10 was used for these batches.

**Table 3: Evaluation of physicochemical parameters of oral disintegrating tablets of zaleplon**

Formulation	Weight variation (mg)	Hardness (Kp)	Thickness (mm)	Friability (%)	Drug content (%)	In vitro dispersion time	Disintegration time (Sec)	Wetting time
F1	200±2	4.5±1.5	3.06±0.6	0.312	101±2	155	93±6	59±3
F2	201±2	4.4±1.6	3.05±0.6	0.326	101±2	126	61±9	39±2
F3	200±3	4.5±1.4	3.06±0.6	0.412	100±2	61	29±3	18±2
F4	199±3	4.5±1.5	3.04±0.7	0.421	99±2	24	15±3	10±2
F5	199±2	4.4±1.6	3.06±0.6	0.436	100±3	26	16±3	12±2
F6	200±2	4.5±1.5	3.07±0.5	0.418	100±2	19	12±2	9±3
F11	200±2	4.4±1.5	3.06±0.5	0.416	100±2	18	12±2	9±2

In the first few attempts (F1 and F2), wet granulation with binder was performed for drug distribution and for granules prior to compression into tablets. Batches F1 and F2 showed good granular nature, flow properties, good content uniformity and mechanical integrity, but the disintegration time was a little longer than the other batches. *In vitro* release studies were carried out using USP

XXVII tablet dissolution test apparatus paddle method at 37±0.5°C, taking 900ml of deionized water as dissolution medium. Speed of rotation of the paddle was set at 75 rpm. 10ml dissolution sample were withdrawn after 5, 10, 15 and 30min and analyzed HPLC. The *in vitro* dissolution profile (Fig. 1) indicated faster and maximum drug release from formulation F5 and F11.

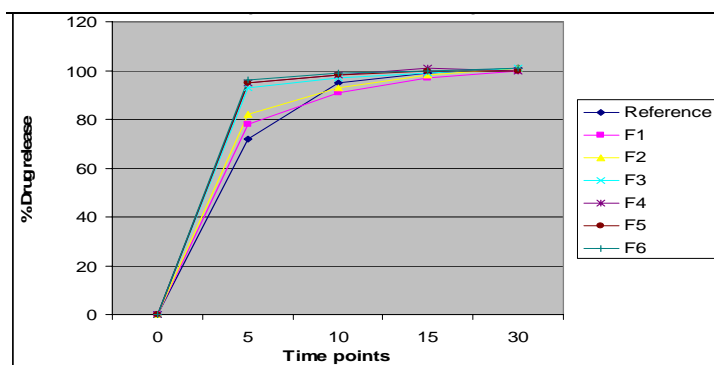


Fig. 1: In vitro drug release of zaleplon

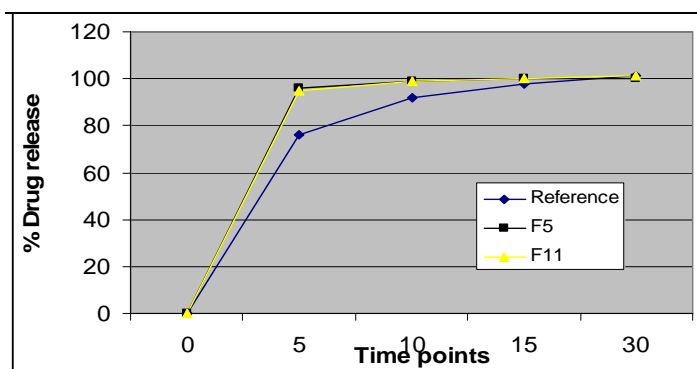


Fig. 2: Dissolution comparison of Reference (Sonata 10 mg - IR capsules) Vs ODT test product

Formulations F5 and F11 were prepared by direct compression with 8.0% polyplasdone XL10. The final tablets were showed release 96% drug at the end of 5min and 100% at the end of 15min when compared to other batches tablets. The rapid drug dissolution might be due to easy breakdown of particles due to porous structure formation by direct compression of blend and rapid absorption of drugs into the dissolution medium.

Reference product was not available for this ODT formulation, but reference product was available for zaleplon (Brand name is Sonata 5 and 10mg) as an IR capsule form. The ODT in house tablets were shown higher drug release in first 10 min time point. Based on the above data, the ODT formulation shown lesser disintegration time and higher dissolution rate (Fig. 2).

Total eight batches were prepared and conducted for taste evaluation study, in that one was positive control (which contain all ingredients except drug), six formulas were test products and one formula was negative control (which contain all ingredients except taste and flavor enhancers like aspartame, acesulfame potassium and peppermint flavor).

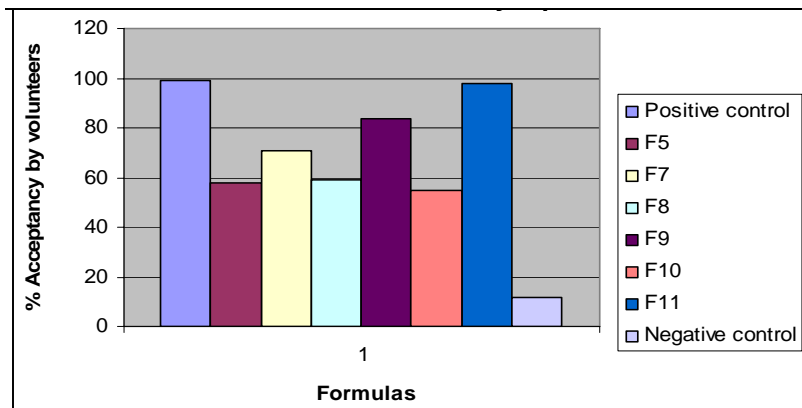
The batches F5, F7 and F8 were prepared using Peppermint Flavor at different concentration to study its effect on patient acceptability in terms of flavor. The flavor concentration depended on the amount

Peppermint Flavor present in tablets (1.0%, 1.8% or 2.7%). The batches F5, F9, F10 and F11 were prepared using aspartame and acesulfame potassium at different concentration to study its effect on patient acceptability in terms of taste and mouth feel. The sweetener concentration depended on the amount aspartame and acesulfame potassium present in tablets.

Formulation F11 was prepared with 1.8% peppermint flavor, 2.0% aspartame, 3.5% acesulfame potassium and volunteers acceptability of this formulation were significantly similar with positive control in terms of mouth feel, taste, flavor and disintegration. Formulation F5 was prepared with 1.0% peppermint flavor, 1.2% aspartame, 2.7% acesulfame potassium and volunteer's acceptability was significantly different with positive control in terms of mouth feel, taste and flavor. Formulation F8 was prepared with 2.7% peppermint flavor, 1.2% aspartame, 2.7% acesulfame potassium and acceptability was significantly different with positive control in terms of mouth feel, taste and flavor. Formulation F10 was prepared with 1.8% peppermint flavor, 1.5% aspartame, 2.0% acesulfame potassium and acceptability was significantly different with positive control in terms of mouth feel and taste. Based on the patient evaluation study, taste and flavor enhancers were not sufficient in formulation F5, F8 and F10, the quantities were sufficient for formulation F11 (Table 4 and Fig. 3). Hence for zaleplon ODT, formulation F11 was finalized.

Table 4: Overall summary report of taste evolution study report

Sr. No.	Formulations	Average points by volunteers	Acceptability	Rank
1	Positive control	99	Very Good	1
2	F5	58	Poor	6
3	F7	71	Acceptable	4
4	F8	59	Poor	5
5	F9	84	Good	3
6	F10	55	Poor	7
7	F11	98	Very Good	2
8	Negative control	12	Worst	8



**Fig. 3: Graphical representation of taste evaluation study report**

The results shown in Table 4 and Fig. 3 indicate that concentration dependent acceptability was observed in batches prepared using peppermint flavor as a flavor enhancing agent and Acesulfame potassium, aspartame as a taste enhancing agents are responsible for good acceptability by volunteers. It is worthwhile to note that as the concentration of Peppermint Flavor increased up to 1.8%, the acceptability also increased.

#### CONCLUSION

Oral disintegrating tablets (ODT) of zaleplon is successfully prepared by using direct compression method, Undoubtedly the availability of various technologies and the manifold advantages of ODT will surely enhance the patient compliance, low dosing, rapid onset of action, fast disintegration, low side effect, good stability and its popularity in the near future. From the study, it can be concluded that direct compression method showed better disintegration and taste masked with help of taste enhancers. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the patient compliance and the absorption leading to its increased bioavailability. Direct compression technique would be an effective and simple alternative approach compared with the use of more expensive process and adjuvant in the formulation of oral disintegrating tablets.

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