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Formulation and Evaluation of Orally Disintegrating Tablets of Zolpidem Tartarate

S. Rajeshwari*, Soma Sekhar. G, Nazemoon.R, Razia Sultana, Hamshida .P. Khanam, M.BiBi. Fathima

Safa college of Pharmacy, Kurnool, Andhra Pradesh, India

A B S T R A C T

Zolpidem tartarate is a super disintegrating tablet. It achieves rapid dissolution, absorption and further improving the bioavailability of drug. It is formulations by in-vitro method and to select the best formulation .Taste of pharmaceutical product is an parameter. Zolpidem Tartarate Oral Disintegrating Tablets were prepared by direct compression method using crosspovidone, croscarmellose sodium, sodium starch glycolate and combinations of CP+CCS, and CP + SSG as superdisintegrants exhibited good preformulation and tabletting properties. The Preformulation studies by bulk density, tapped density.

Keywords: Super disintegrating tablet, solid dispersion

A R T I C L E I N F O

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***Corresponding Author**
S. Rajeshwari
Department of pharmaceutics
Safa College of pharmacy
Kurnool, Andhra Pradesh, India.
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1. Introduction

Oral administration is the most popular route about 50-60% of total dosage forms are administered due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly patient compliance. Solid oral delivery systems do not require sterile conditions and are therefore less expensive to manufacture[1].One important drawback of solid dosage forms is the difficulty in swallowing (dysphasia) or chewing in some patients particularly pediatric and geriatric patients[2].Oral fast dissolving drug delivery system (OFDDS) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self-administration without water or chewing[3]. Orally disintegrating tablets are also called as mouth-dissolving

tablets, fast disintegrating tablets, fast dissolving tablets, oral dispersible tablets, rapimelts, porous tablets, quick dissolving tablet[4]. The US Food and Drug Administration 2008 publication of guidance for industry: Orally Disintegrating Tablets. Three main points stand out in the final guidance[5]:

- ODTs should have an *In vitro* disintegration time of approximately 30 s or less (using United States Pharmacopeia disintegration test or equivalent).
- Generally, the ODT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an ODT for both patients and regulators.
- The guidance serves to define the upper limits of the ODT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an ODT.
- Freeze drying of drug along with additives imparts glossy amorphous structure resulting in highly porous and light weight product[3].

The tablets prepared by lyophilization disintegrate rapidly in less than 5 sec due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat sensitive drugs i.e. thermo-labile substances[11]. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions[7].

Ideal properties of ODTs [6, 7]

- Require no water for oral administration, yet dissolve/disperse/ disintegrate in mouth in a matter of seconds. Have a pleasing mouth feel.
- Have an acceptable taste masking property.

Advantages of ODTs [7, 8]

- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.

Limitations of ODTs[9]

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
  The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly

Formulation aspects in developing ODTs[3]

Orally disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and ODTs formed vary in various properties such as

1. Mechanical strength of tablets
2. Taste and mouth feel
3. Swallow ability
4. Drug dissolution in saliva
5. Bioavailability
6. Stability

Techniques in Preparation of Orally Disintegrating Drug Delivery System [7, 11]

1. Freeze drying or Lyophilization
2. Spray drying
3. Molding
4. Phase transition process
5. Melt granulation
6. Sublimation

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Superdisintegrants

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[9].

Nanonization[8]

A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poorly water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

Mechanism of Super Disintegrants [7]

There are major mechanisms for tablets disintegration as follows

Swelling: Perhaps the most widely accepted general mechanism of action for tablet disintegration isswelling. Tablets with high porosity show poor disintegration due to lack of adequate swellingforce. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It isworthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in thetablet and disintegration is again slows down.

Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'nonswellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking [**7, 9]**

Due to deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was

improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

2. Materials and Methods

Materials: Zolpidem tartarate was a gifted sample from Hetero Drugs, Hyd, Crosspovidone, Croscarmellose sodium, Sodium starch glycolate, Avicel PH 102, Sodium stearyl fumerate, Pearlitol SD 200, Sodium saccharin, Orange flavor were purchased from hetero drugs, hyd, Methanol ,Sodium hydroxide were purchased from ahmedabad, Potassium dihydrogen orthophosphate purified, Eosin ,were purchased from S D Fine chemicals limited ,mumbai.

Methods:

Evaluation of orally disintegration tablet formulations

Different quality control tests were performed for all the ODT formulations to check whether these have met the specifications given in USP along with other *In- vitro* tests like wetting time and water absorption ratio.

***In-Vitro* Studies**

Wetting time and Water absorption ratio (R)

Method: Five circular tissue papers were placed in a petridish with a 10-cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petri dish. The dye solution is used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the petri dish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in replicates (n=6). The wetting time was recorded using a stopwatch.

Disintegration Time

Disintegration time is considered to be one of the important criteria in selecting the best formulation. To achieve correlation between disintegration time *In vitro* and *In vivo* (in oral cavity) several methods were proposed, developed and followed at their convenience.

3. Results and Discussions

The overall objective of this study was to design oral disintegrating Zolpidem Tartarate tablets and films that disintegrate or disperse in the saliva within a matter of seconds.

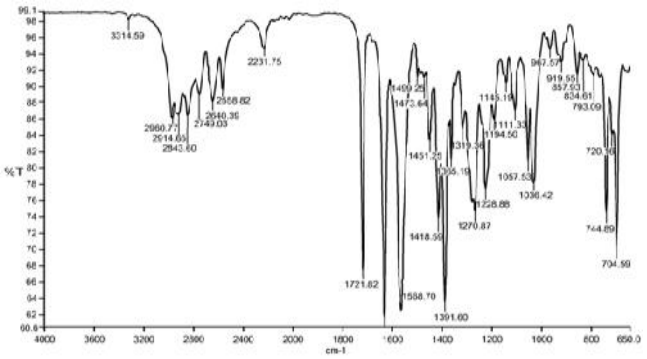

Figure 1: FTIR Spectra

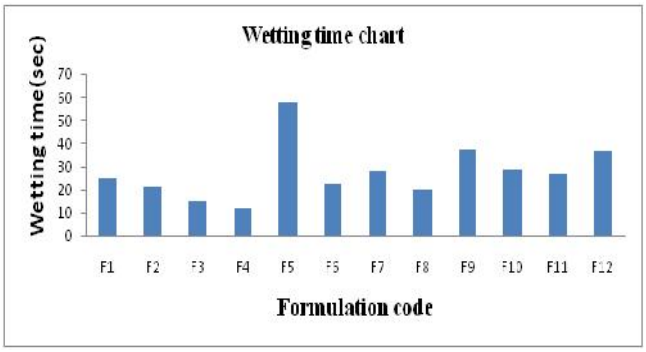

Figure 2: Graphical representation of wetting time of Zolpidem Tartarate ODTs prepared by varying concentrations of superdisintegrants

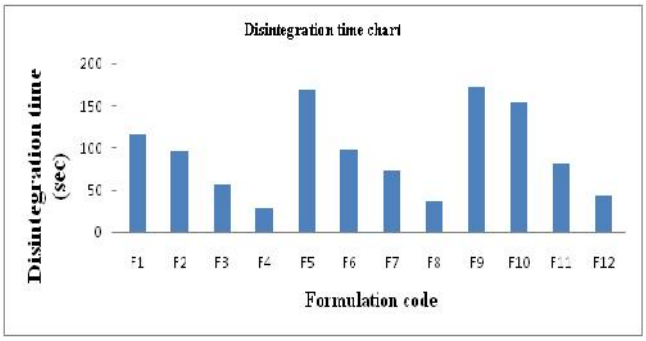

Figure 3: Graphical representation of disintegration times of Zolpidem Tartarate ODTs prepared by varying concentrations of superdisintegrants

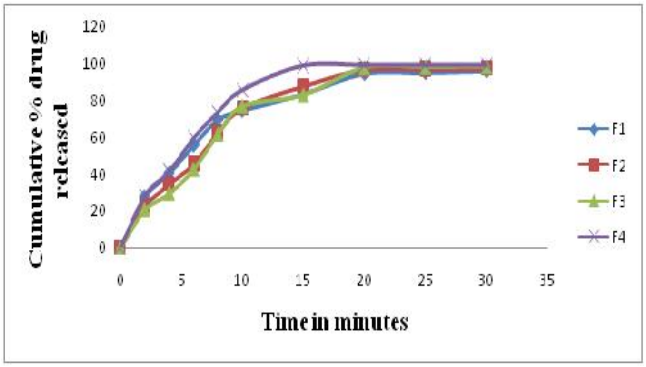

Figure 4: Graphical representation of Cumulative percent Zolpidem Tartarate released from ODTs containing varying concentrations of crosspovidone.

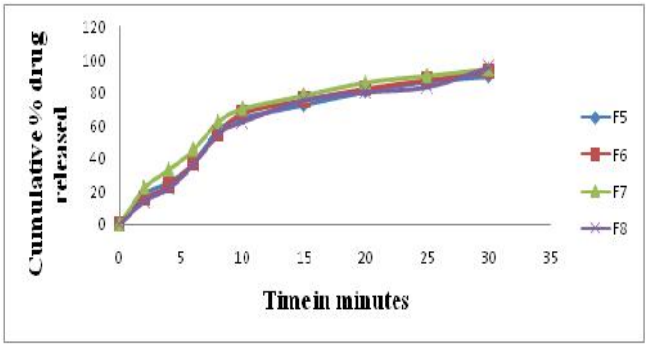

Figure 5: Graphical representation of Cumulative percent Zolpidem Tartarate released from ODTs containing varying concentrations of croscarmellose sodium.

Table 1: Standard graphics of zolpidem tartarate

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Compressibilty index (%)	Angle of repose (ɵ)
F1	0.435	0.522	1.20	16.66	32.67
F2	0.429	0.518	1.20	17.18	29.08
F3	0.430	0.524	1.21	17.93	31.78
F4	0.432	0.528	1.22	18.18	30.64
F5	0.428	0.518	1.21	17.37	30.36
F6	0.420	0.510	1.21	17.64	31.05
F7	0.416	0.509	1.22	18.27	32.54
F8	0.417	0.515	1.23	19.02	29.67
F9	0.425	0.515	1.21	17.47	31.85
F10	0.421	0.509	1.20	17.28	29.56
F11	0.419	0.515	1.22	18.64	30.17
F12	0.415	0.512	1.23	18.94	32.08

Table 2: Tabletting characteristics of Zolpidem Tartarate ODTs

Formulation	Wetting time (sec)	*In vitro* dispersion time (sec)	Disintegration time (sec)	Water absorption ratio (%)
F1	24.83±0.98	221.33±1.03	116.5±1.37	58.45
F2	21.16±0.75	180.5±1.04	95.16±0.75	59.25
F3	14.66±0.51	75±0.89	56.50±1.64	58.9
F4	**11.66±0.51**	**54±0.63**	**27.83±1.16**	**60.65**
F5	57.33±0.81	244.5±1.04	168.83±1.94	59.88
F6	22.33±1.36	215.5±0.54	98±0.63	61.48
F7	28±1.09	177.83±1.16	73.16±1.47	59.55
F8	19.66±0.81	126.66±0.81	36.66±1.21	60.01
F9	37.33±0.81	259.83±1.47	171.83±1.16	64.37
F10	28.33±0.81	225.33±0.81	153±0.89	67.54
F11	26.66±0.81	186.83±0.75	81.5±1.04	65.50
F12	36.83±1.16	154.5±0.83	42.66±1.75	65.89

Table 3: *In-vitro* dispersion time

Formulation	Weight (mg)	Drug content (%)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)
F1	99.9±0.70	98.96±0.47	3.05±0.13	0.48	3.84±0.032
F2	99.52±0.85	99±0.65	3.10±0.15	0.53	3.85±0.028
F3	98.9±0.52	99.11±0.52	2.95±0.08	0.44	3.86±0.024
F4	100.2±1.17	99.15±0.60	2.95±0.10	0.57	3.86±0.051
F5	99.0±0.49	99.2±0.4	3.08±0.12	0.43	3.88±0.048
F6	98.8±0.58	98.85±0.58	3.11±0.14	0.56	3.90±0.052
F7	99.3±0.54	99.31±0.24	2.92±0.08	0.53	3.92±0.038
F8	100.4±1.0	98.96±0.28	3.0±0.09	0.45	3.91±0.042
F9	99.6±0.95	99.3±0.38	2.9±0.07	0.6	3.90±0.040
F10	99.2±0.97	99.36±0.29	3.05±0.08	0.49	3.89±0.042
F11	99.4±0.86	98.75±0.40	3.05±0.09	0.53	3.89±0.034
F12	98.5±0.42	99.21±0.38	2.93±0.08	0.58	3.87±0.031

Table 4: Cumulative percent Zolpidem Tartarate released from ODTs containing varying concentrations of different superdisintegrants

Cumulative percent (±S.D.) drug released						
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
2	27.35±0.28	22.35±0.52	20.46±0.25	28.31±0.23	18.35±0.34	15.43±0.30
4	40.33±0.28	34.36±0.28	29.28±0.19	41.33±0.24	25.5±0.28	23.43±0.32
6	55.46±0.31	45.31±0.27	42.35±0.25	59.33±0.26	37.36±0.25	37.36±0.26
8	69.46±0.27	62.35±0.25	61.31±0.23	73.48±0.34	57.41±0.23	54.38±0.26
10	74.38±0.27	75.48±0.30	76.4±0.36	85.38±0.34	64.55±0.28	67.38±0.37

15	83.35±0.20	87.4±0.31	82.53±0.30	98.6±0.29	72.48±0.35	75.46±0.26
20	94.45±0.30	96.31±0.29	97.31±0.20	98.89±0.32	80.45±0.28	82.31±0.23
25	94.89±0.24	96.57±0.28	97.76±0.28	98.95±0.24	86.5±0.26	87.48±0.24
30	95.78±0.27	96.85±0.32	97.96±0.25	98.99±0.23	89.53±0.19	92.36±0.25

Table 5: Formulae of Zolpidem Tartarate ODTs prepared with combination of superdisintegrants

Ingredients	CP + CCS				CP + SSG			
	6%	8%	10%	12%	6%	8%	10%	12%
Zolpidem Tartarate	5	5	5	5	5	5	5	5
Superdisintegrants	3	6	9	12	3	6	9	12
Avicel PH 102	69	58	49	38	69	58	49	38
Pearlitol SD200	10	10	10	10	10	10	10	10
Sucralose	10	10	10	10	10	10	10	10
Orange flavor	2	2	2	2	2	2	2	2
Sodiumstearyl fumerate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Colloidal silica	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total weight (mg)	100	100	100	100	100	100	100	100

Note: CP – Crosspovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate

4. Conclusion

The present works involves formulation and development and optimization and in-vitro evaluation of zolpidem tartarate tablet with fixed dose of sustained release. Under pre formulation studies API (Active pharmaceutical ingredients) Characterization and drug excipients compatibility studies carried out. The polymers and other excipients were selected based on the satisfying results produced during drug excipients compatibility studies develop the final formulation. The final suitable formulation was achieved by the direct compression method.

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