ejpmr, 2023, 10(8), 391-397

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION, DEVELOPMENT AND IN VITRO EVALUATION OF ZOLPIDEM TARTRATE IMMEDIATE RELEASE TABLETS

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Article Received on 04/06/2023 **Article Revised on 24/06/2023** **Article Accepted on 14/07/2023**

ABSTRACT

The aim of the present study is to develop and evaluate the immediate release tablet of Zolpidem tartrate by direct compression method. The superdisintegrant Crospovidone, Croscarmellose sodium and Fenugreek were used for immediate release of drug from tablet. The prepared tablets were evaluated for all pre-compression parameters and post-compression parameters. The drug excipients interaction was investigated by FTIR. All formulation showed compliances with Pharmacopoeial standards. The study reveals that formulations prepared by direct compression F6 exhibit highest dissolution using Croscarmellose sodium showed faster drug release 99.18% over the period of 45min while disintegration time of the tablet was showed 15 sec comparison to other formulations of Zolpidem tartrate.

KEYWORDS: Zolpidem tartrate, Crospovidone, Croscarmellose sodium, Fenugreek superdisintegrant and Immediate release tablet.

INTRODUCTION

Oral route is the most convenient and extensively used for drug administration. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance suitable for industrial production, improved stability and bioavailability. The concept of immediate release tablets emerged from the desire to provide patient with more conventional means of taking their medication when emergency treatment is required. Recently, immediate release tablets have gained prominence of being new drug delivery systems. The oral route of administration has so far received the maximum attention with respect to research on physiological and drug constraints as well as design and testing of product, Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic. Several orally disintegrating tablet (ODT) technologies based on direct compression. In pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation is at least 70% (preferably 80%) of active ingredient within 4 hours, such as within 3 hours, preferably 2 hours, more preferably within 1.5 hours, and especially within an hour (such as within 30 minutes) of administration. In Formulation of immediate release the commonly Superdisintegrants used are Croscarmellose, sodium, Sodium Starch glycolate and Crospovidone.[1]

Oral route of administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems does not need sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. There is requirement for new oral drug delivery system because of poor patient acceptance for invasive methods, requirement for investigation of new market for drugs and combined with high cost of disease management. Developing new drug delivery techniques and that utilizing in product development is critical for pharma companies to survive this century.[2,3,4]

The term ‘immediate release’ pharmaceutical formulation is the formulation in which the rate of release of drug and/or the absorption of drug from the formulation, is neither appreciably, nor intentionally, retarded by galenic manipulations. Immediate release dosage form is those which break down quickly and get dissolved to release the medicaments. In the present case, immediate release may be provided of an appropriate pharmaceutically acceptable diluent or carrier, which

diluent or carrier does not delay, to an appreciable extent, the rate of drug release and/or absorption.[5,6,7]

Immediate release drug delivery is suitable for drugs having long biological half-life, high bioavailability, lower clearance and lower elimination half-life. But main requirement for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat undesirable imperfection or disease.[8]

Pharmacokinetics

It is the study of absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution is fast. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

Pharmacodynamic[9]

- ✓ Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ.
- ✓ Decreased ability of the body to respond reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.
- ✓ Decreased sensitivity of the CVS to α-adrenergic agonist and antagonist.
- ✓ Immunity is less and taken into consideration while administered antibiotics.
- ✓ Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates.
- ✓ Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.

Research workers have clinically evaluated drug combination for various classes cardiovascular agents, diuretics, anti-hypertensive etc. for immediate release dosage forms. The combination choice depends on disease state of the patient.

Merits[15]

1. Unit dose system and Long shelf life.
2. Cost effective.
3. Improved stability, bioavailability.
4. Accuracy and uniformity of drug content.
5. More Economic and Ease of administration.
6. Tastelessness and Elegance.
7. Patient compliance.
8. They are in general the easiest and cheapest to package.
9. Optimal drug dissolution and hence, availability from the dosage form for absorption consistent with intended use.

Demerits[15]

1. Posses swallowing difficulty.
2. Onset of action is slow and depends on disintegration and dissolution. Some drugs resist compression, due to their amorphous nature or low-density.
3. Drugs having bitter taste, objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating of tablet Bioavailability problems.
4. Chance of GI irritation caused by locally high concentrations medicaments.

Desired criteria for immediate release drug delivery system

Immediate release dosage form should In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.

- ✓ In the case of liquid dosage form it should be compatible with taste masking.
- ✓ Be portable without fragility concern.
- ✓ Have a pleasing mouth feel.
- ✓ It should not leave minimal or no residue in the mouth after oral administration.
- ✓ Exhibit low sensitivity to environmental condition as humidity and temperature.
- ✓ Be manufactured using conventional processing and packaging equipment at low cost.
- ✓ Rapid dissolution and absorption of drug,which may produce rapid onset of action.

MATERIALS

Zolpidem Tartrate Procured From Tripada Pharmaceuticals Ltd., Ahmedabad, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad. Crospovidone (Merck Specialities Pvt Ltd), Croscarmellose sodium (Merck Specialities Pvt Ltd), Fenugreek (Merck Specialities Pvt Ltd), MCC (Merck Specialities Pvt Ltd), Aspartame (Merck Specialities Pvt Ltd), Mg stearate (Merck Specialities Pvt Ltd), Talc Merck Specialities Pvt Ltd.

METHODOLOGY

Buffer preparation

Preparation of 0.2M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm sodium hydroxide pellets were dissolved 1000ml of distilled water and mixed.

Preparation of pH 6.8 Phosphate buffer: Accurately measured 250ml of 0.2M potassium Dihydrogen orthophosphate and 112.5 ml 0.2M NaOH was taken into

the 1000ml volumetric flask. Volume was made up to 1000ml with distilled water.

Analytical method development for zolpidem tartrate

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 296 nm. Hence all further investigation was carried out at the same wavelength.

b) Preparation of Standard graph in pH 6.8 phosphate buffer

100 mg of Zolpidem tartrate was dissolved in 100ml of Phosphate buffer of pH 6.8., form primary stock 10ml was transferred to another volumetric flask made up to 100ml with Phosphate buffer of pH 6.8, from this secondary stock was taken separately and made up to 10 ml with Phosphate buffer of pH 6.8, to produce 10, 20, 30, 40 and 50µg/ml respectively. The absorbance was measured at 296 nm by using a UV spectrophotometer.

Formulation development

Drug and different concentrations for super Disintegrates and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes. The obtained blend was lubricated with Magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 minutes. The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zolpidem tartrate	5	5	5	5	5	5	5	5	5
Crospovidone	5	10	15	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	5	10	15	-	-	-
Fenugreek	-	-	-	-	-	-	5	10	15
Mcc	71	66	61	71	66	61	71	66	61
Aspartame	10	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4	4
Total weight of tablet (mg)	100	100	100	100	100	100	100	100	100

Total weight of tablets = 100 mg

RESULTS AND DISCUSSION

Determination of λ_{max}

The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 296nm.

Calibration curve of zolpidem tartrate

The standard curve of Zolpidem tartrate was obtained and good correlation was obtained with R^2 value of 0.998, the medium selected was pH 6.8 phosphate buffer.

Table 1: Standard graph values of zolpidem tartrate at 296 nm in pH 6.8 phosphate buffer.

Concentration (µg/ml)	Absorbance
0	0
10	0.157
20	0.302
30	0.418
40	0.572
50	0.698

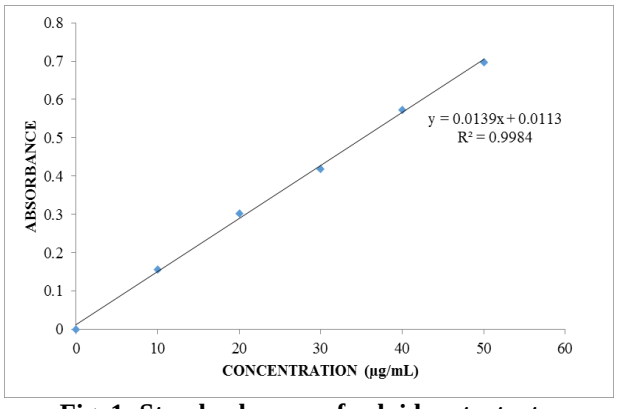

Fig. 1: Standard curve of zolpidem tartrate.

Evaluation

Characterization of precompression blend

Table 2: Physical properties of precompression blend.

Formulation code	Angle of repose (Ɵ)	Bulk density (gm/cm^3	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	19.66±0.538	0.555±0.304	0.598±0.018	8.695	1.095
F2	22.7±0.933	0.524±0.141	0.593±0.334	11.11	1.133
F3	25.08±0.198	0.598±0.061	0.657±0.431	11.76	1.333
F4	21.39±0.567	0.502±0.654	0.598±0.318	17.39	1.121
F5	24.46±0.338	0.511±0.341	0.593±0.734	25.00	1.333
F6	26.75±0.735	0.574±0.3115	0.673±0.533	9.52	1.105
F7	22.12±0.244	0.582±0.758	0.641±0.290	12.50	1.142
F8	24.23±0.259	0.521±0.0534	0.581±0.941	11.53	1.130
F9	25.33±0.363	0.551±0.0821	0.555±0.304	22.22	1.285

All the values represent n=3

Evaluation of tablets

Physical evaluation of zolpidem tartrate immediate release tablets

The results of the weight variation, hardness, thickness, friability and drug content of tablets are given in table 10.3. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limit. The hardness of the tablets ranged from 4.1- 5.6 kg/cm^2 and the friability values were < than 0.68 % indicating that the tablets were compact and hard. The thickness of the tablets ranged from 3.11- 3.87 mm. All the formulations satisfied the content of the drug as they contained 97.24-99.21 % of Zolpidem tartrate and good uniformity in drug content was observed. Thus all physical attributes of the prepared tablets were found to be practically within control limits.

Table 3: Physical evaluation of zolpidem tartrate.

Formulation code	Weight variation (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content Uniformity (%)	Disintegration Time (Sec)
F1	99.25	2.25	3.1	0.36	98.70	36
F2	98.82	2.69	3.9	0.51	97.24	32
F3	100.12	2.14	3.8	0.48	99.21	25
F4	99.68	2.54	3.1	0.61	98.10	39
F5	100.17	2.87	3.7	0.40	98.21	22
F6	98.52	2.90	3.6	0.36	97.96	15
F7	100.06	2.11	3.3	0.39	98.41	43
F8	98.32	2.70	3.9	0.28	97.50	36
F9	99.16	2.83	3.0	0.18	98.44	30

Figure 2: Disintegration test (Sec).

***In vitro* release studies**

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37±0.5 ˚C. Samples of 5 ml were collected at different time intervals up to 1 hr and has analyzed after appropriate dilution by using UV spectrophotometer at 296 nm.

Table 4: *In vitro* dissolution data for formulation F1-F9.

Time (min)	% of drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	15.85	20.16	28.32	16.43	23.91	31.10	15.15	26.78	30.61
10	21.93	28.27	31.15	28.52	32.64	42.29	28.99	34.12	39.52
15	38.60	44.51	42.92	33.01	39.20	58.35	39.16	50.59	47.90
20	49.18	62.73	67.80	45.10	60.09	66.63	45.29	58.60	65.13
25	57.23	70.96	76.12	56.28	76.60	73.55	60.31	69.14	77.05
30	65.71	78.32	85.05	75.36	85.14	89.16	67.90	78.22	84.34
45	76.53	83.18	92.73	82.62	92.21	99.18	80.56	87.63	90.28

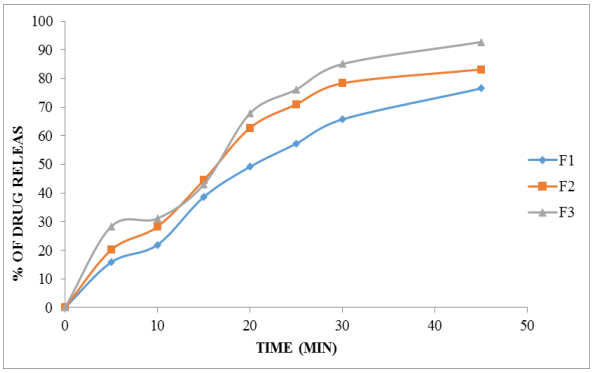

Fig. 3: *In vitro* dissolution data for formulation F1-F3.

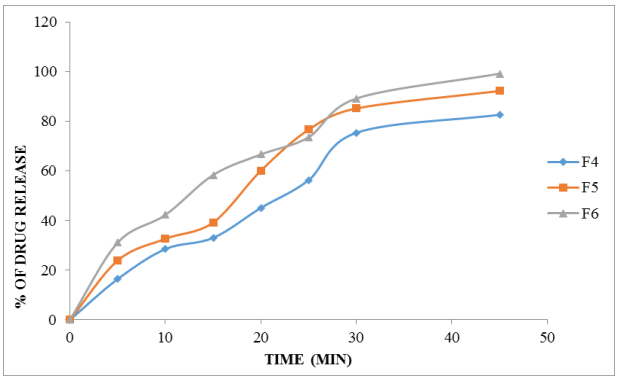

Fig. 4: *In vitro* dissolution data for formulations F4-F6.

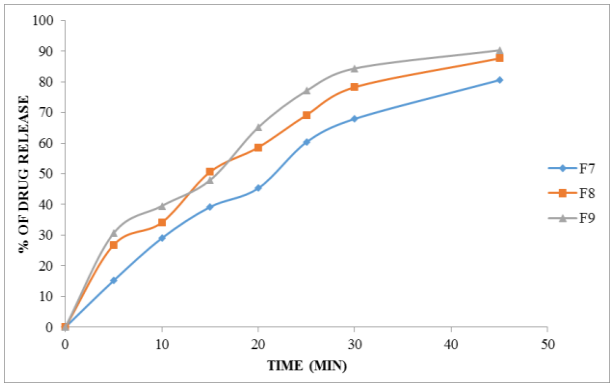

Fig. 5: *In vitro* dissolution data for formulations F7-F9.

From the table it was evident that the formulation prepared with Crospovidone were showed good drug release i.e., F3 formulation (92.73%) in higher concentration of blend i.e. 15 mg. Formulations prepared with Croscarmellose sodium showed good drug release i.e., 99.18 % (F6 formulation) in 15 mg concentration. When increase in the concentration of Croscarmellose sodium drug release increased. Formulations prepared with Fenugreek showed maximum drug release i.e., 90.28% (F9 formulation) at 45 min in 15 mg of blend.

Among all formulations F6 considered as optimized formulation which showed maximum drug release at 45 min i.e., 99.18 %. Croscarmellose sodium showed good release when compared to Crospovidone and Fenugreek. Finally concluded that F6 formulation contains Croscarmellose sodium was optimized formulation.

Drug-Excipient compatibility studies by FTIR studies

Zolpidem tartrate was mixed with various proportions of excipients showed no colour change at the end of two months, providing no drug –excipients interactions.

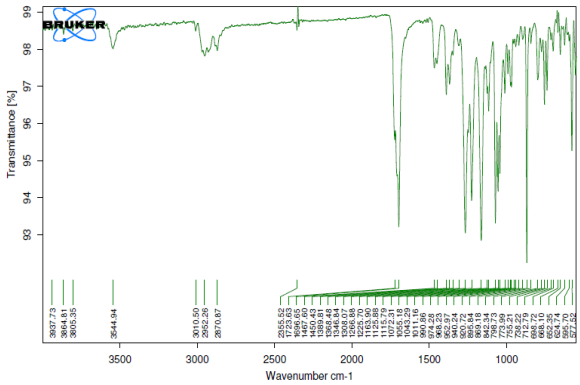

Fig. 6: FTIR spectra of pure drug.

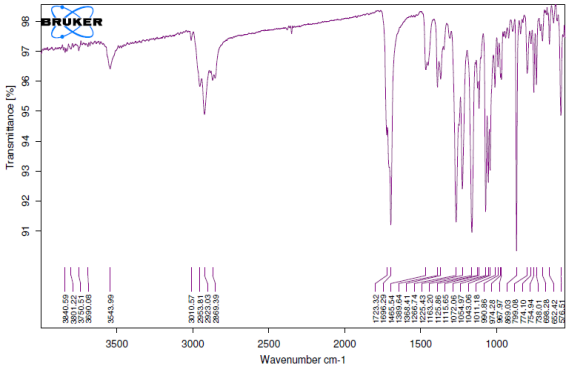

Fig. 7: FTIR spectra of optimized formulation.

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Zolpidem tartrate and excipients used in the preparation of different Zolpidem tartrate Immediate Release formulations. Therefore the drug and excipients are compatible to form stable.

CONCLUSION

Preformulation studies of Zolpidem tartrate were performed; the FT-IR analysis revealed that the superdisintegrants and excipients used were compatible with Zolpidem tartrate. Immediate release tablets of Zolpidem tartrate are to be prepared by direct compression technique using superdisintegrants, namely Crospovidone, Croscarmellose sodium and Fenugreek. Amongst all the formulations, formulation containing Croscarmellose sodium as superdisintegrants is fulfilling all the parameters satisfactorily. It has shown excellent *in vitro* disintegration compared to other superdisintegrants. Combines multiple mechanisms to achieve disintegration at low levels without forming gel i.e. require slow dissolution, disintegration and provides rapid disintegration in direct compression tablet as well increases tablet breaking force and reduces friability; enhances the dissolution of poorly soluble drugs. Apart from all the formulations, F6 formulation showed maximum drug release (99.18%) at the end of 45 min.

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