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Original Article

Formulation development and in vitro evaluation of immediate release tablets of zolpidem tartrate

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ABSTRACT

Zolpidem Tartarate belongs to class II drugs, that is, characterized by low solubility and high permeability therefore, the enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects. The pre-compression blend of Zolpidem Tartarate soild dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** The pre-compression blend of all the batches indicates well to fair flowability and compressibility. Solid dispersions were prepared with various concentrations of carriers, the prepared solid dispersions were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. Among all the formulations F2 formulation containing, Drug and β cyclodextrin in the ratio of 1:2 showed good result that is 97.06 % in 20 minutes. Hence from the dissolution data it was evident that F2 formulation is the better formulation .By conducting further studies like *Invivo* studies, preclinical and clinical studies we can commercialize the product.

Keywords: Zolpidem Tartarate, solid dispersions, β cyclodextrin

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INTRODUCTION

General Introduction:[1] Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process. For many drug substances, conventional immediate-release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient.

Current technologies in oral drug delivery:[4] Over the last 3 decades, many novel oral drug therapeutic systems have been invented along with the appreciable development of drug delivery technology. Although these advanced DDS are manufactured or fabricated in traditional pharmaceutical formulations, such as tablets, capsules, sachets, suspensions, emulsions, and solutions, they are superior to the conventional oral dosage forms in terms of their therapeutic efficacies, toxicities, and stabilities. Based on the desired therapeutic objectives, oral DDS may be sorted into three categories:

- immediate-release preparations,
- controlled-release preparations and
- targeted- release preparations.

Immediate-Release Preparations: These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to dysphasic patients, especially the elderly and bedridden, and new business opportunities. Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, such as sodium carbonate (or sodium bicarbonate) and citric acid (or tartaric acid), and superdisintegrants, such as sodium starch glycolate, crosscarmellose sodium, and crospovidone. Current technologies in fast-dispersing dosage forms include modified tableting systems, shear form technology, which employs application of centrifugal force and controlled temperature, and freeze-drying.

Controlled-Release Preparations: The currently employed CR technologies for oral drug delivery are diffusion-controlled systems; solvent activated systems, and chemically controlled systems. Diffusion-controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate-limiting step, respectively, through a polymer matrix or a polymeric membrane. Solvent-activated systems may be either osmotically controlled or controlled by polymer swelling. Chemically controlled systems release drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from a polymer chain. It is worth mentioning here that the so-called programmed-release (‘‘tailored-release’’) profile of a final CR product is rarely the outcome of a single pharmaceutical principle. Depending on the specific physicochemical properties of the drug in question and desired therapeutic objectives, different formulation and CR principles may be proportionally combined within the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and excipients that incorporate desired principles.

Tablets:[3,5,6] Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of the 19th century and their popularity continues. Tablets remain as a popular dosage form because of the advantages, afforded both to the manufacturer [eg: simplicity & economy of preparation, stability and convenience in packing, shipping, and dispensing] and the patient [eg: accuracy of dosage, compactness, post ability, blandness of taste and ease of administration. Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration.

Properties of tablets: The attributes of an acceptable tablet are as follows:- The tablet must be sufficiently strong and resistance to shock and abrasion and to withstand handling during manufacturing, packing, shipping, and use. Hardness and friability tests measure this property. A Tablet must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation and content uniformity tests. The drug content of the tablet must be bioavailable. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels after its administration. Tablets must be elegant in appearance and must have characteristic shape, color, and other markings necessary to identify the product. Tablets must retain all these functional attributes, which include drug stability and

efficacy. The main aim of the present study is to formulate and evaluate Zolpidem Tartrate Immediate Release Tablets. Objectives of work is to formulate Zolpidem Tartrate Immediate Release Tablets for the improvement of solubility, dissolution rate and to perform various quality control evaluation.

MATERIALS AND METHOD

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

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

Preparation of pH 6.8 phosphate buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 112.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL 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 λmax was found to be 294 nm. Hence all further investigations were 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 methanol 5 ml, volumetric flask make upto 100 ml of Phosphate buffer of pH 6.8 , from this primary stock 10 ml 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 2,4,6,8 and 10 µg/ml respectively. The absorbance was measured at 294 nm by using a UV spectophotometer.

RESULTS & 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 294 nm.

Calibration curve of Zolpidem Tartrate: The standard curve of Zolpidem Tartrate was obtained and good correlation was obtained with R^2 value 0f 0.999.the medium selected was pH 6.8 phosphate buffer. The standard graph values of Zolpidem Tartrate are tabulated as below-

Table1: Standard Graph values of Zolpidem Tartrate at 294 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.198
4	0.396
6	0.601
8	0.804
10	0.998

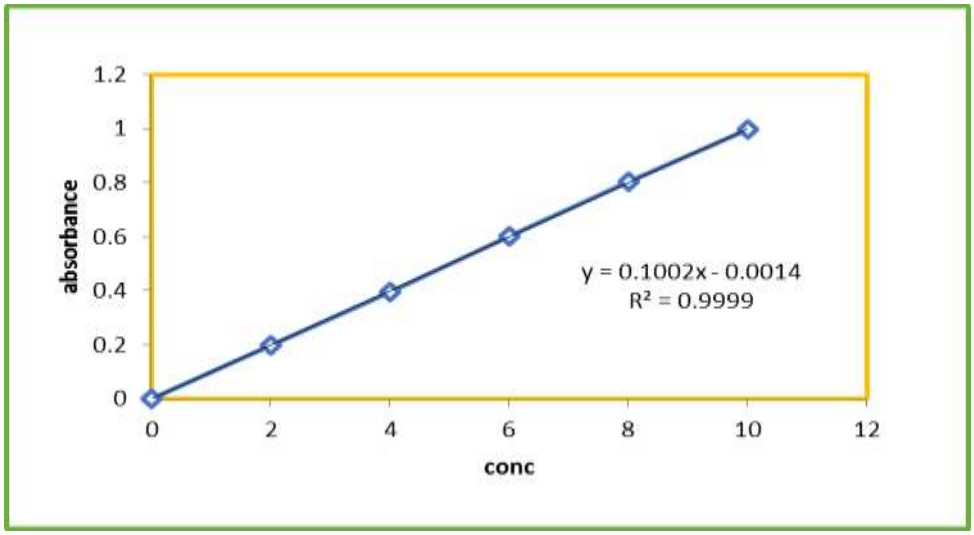

Fig no 1: STANDARD CURVE OF ZOLPIDEM TARTRATE

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, proving no drug-excipient interactions.

Evaluation:

Characterization Of Pre-compression Blend: The pre-compression blend of Zolpidem Tartrate solid dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 28^0, Carr's index values were less than 11 for the pre-compression blend of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Evaluation of Tablets:

Physical Evaluation of Zolpidem Tartrate solid dipersion immeadiate tablets: The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 7.All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 4.6 to 5 kg/cm^2 and the friability values were less than 0.561% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 4.71-4.91cm. All the formulations satisfied the content of the drug as they contained 98-100% of Zolpidem Tartrate and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

***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 hrs and analysed after appropriate dilution by using UV Spectrophotometer at 294 nm.

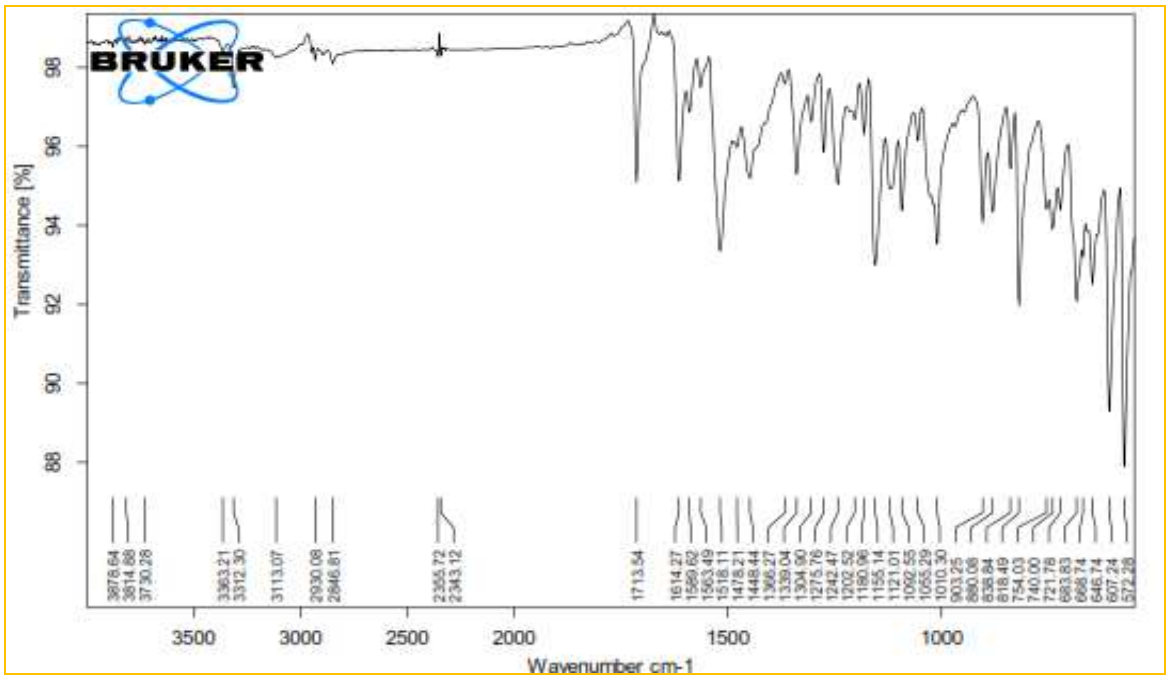

Fig 2 : FTIR SPECTRA OF PURE DRUG

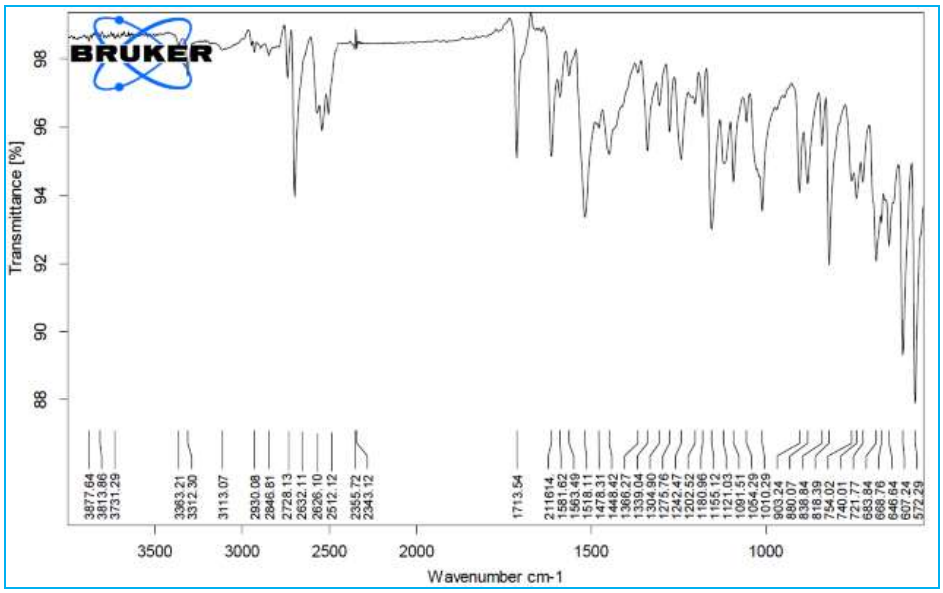

Fig 3 : FTIR SPECTRA OF OPTIMISED FORMULA

Table3 . Physical properties of pre-compression blend

Formulation Code	Angle of repose (Ɵ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	25.10°	0.53	0.59	9.43	1.11
F2	25.43°	0.54	0.60	9.40	1.10
F3	25.41°	0.54	0.58	10.01	1.07
F4	26.40°	0.51	0.61	10.11	1.19
F5	27.12°	0.58	0.63	10.34	1.08
F6	25.31°	0.59	0.64	10.12	1.08
F7	26.11°	0.56	0.63	9.93	1.12
F8	26.15°	0.53	0.58	10.13	1.09
F9	26.10°	0.54	0.61	10.2	1.12

All the values represent mean n=3

Table4 .Physical Evaluation of Zolpidem Tartrate tablets

Formulation code	Average Weight (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity(%)
F1	103.12	4.76	2.5	0.420	99.12
F2	98.56	4.74	2.2	0.341	99.03
F3	99.67	4.71	2.1	0.363	100.01
F4	97.23	4.80	2.1	0.561	100.31
F5	109.09	4.81	2.0	0.482	99.63
F6	105.24	4.74	2.2	0.513	99.41
F7	100.23	4.76	2.2	0.412	97.94
F8	99.73	4.71	2.3	0.432	96.16
F9	98.34	4.73	2.5	0.512	100.15

Table5 :*In vitro* dissolution data for formulations F1 – F3.

Time(MIN)	% Drug release		
	F1	F2	F3
0	0	0	0
5	16.73	26.73	22.56
10	20.4	41.06	46.57
15	45.9	74.9	68.9
20	65.56	97.06	87.73
25	74.9		92.4
30	84.4		

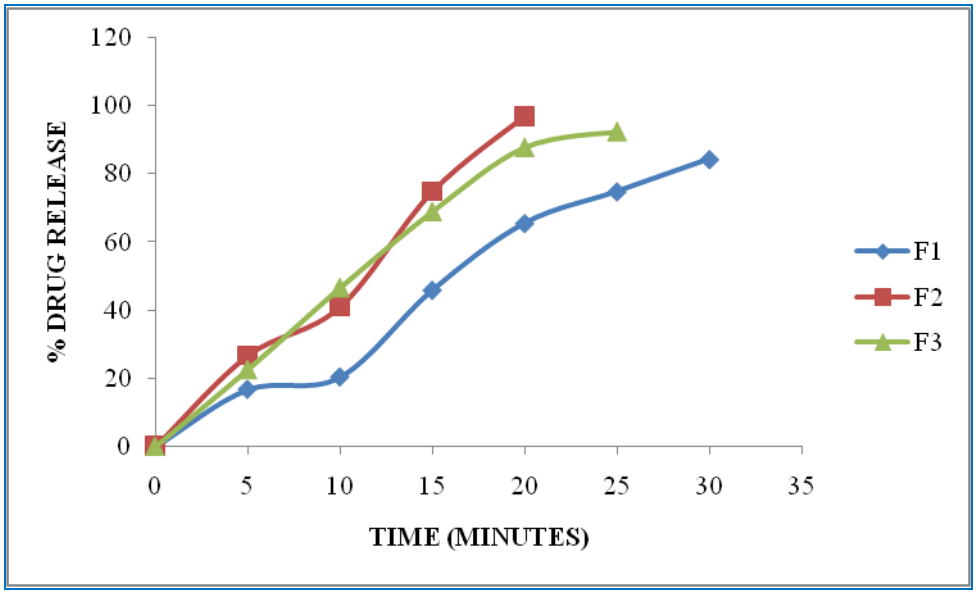

Fig4 : *In vitro* dissolution data for formulations F1 – F3

Table6 :*In vitro* dissolution data for formulations F4– F6

Time (min)	% drug release		
	F4	F5	F6
0	0	0	0
5	28.86	23.18	19.21
10	39.01	41.86	32.60
15	48.16	66.06	56.43
20	60.22	81.44	64.83
25	76.99	99.62	71.32
30	88.81		87.95

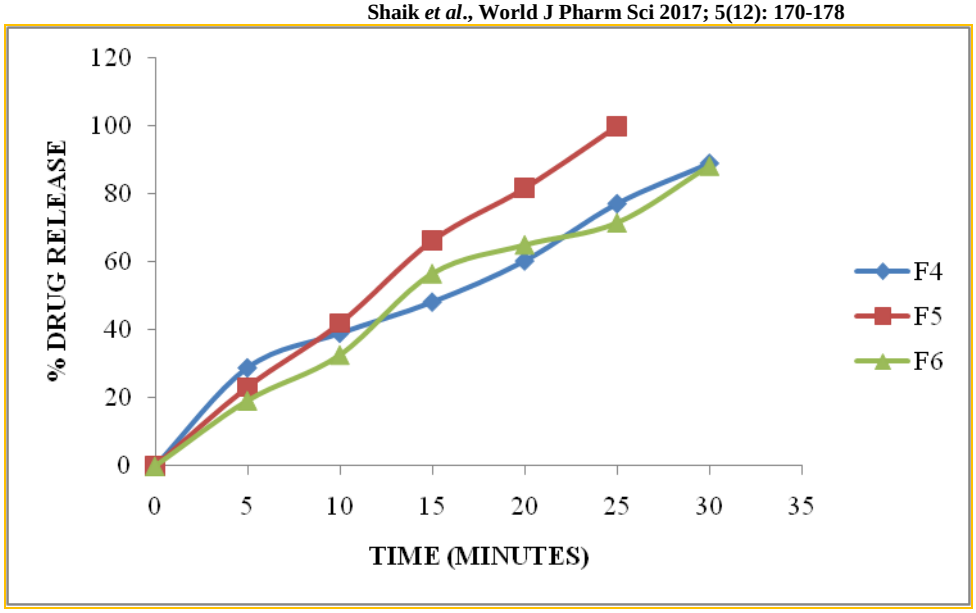

Fig5 : *In vitro* dissolution data for formulations F4 – F6.

Table 7 :*In vitro* dissolution data for formulations F7– F9 .

Time (min)	% drug release		
	F7	**F8**	**F9**
0	0	0	0
5	20.86	26.18	19.21
10	36.01	45.86	22.60
15	41.16	55.06	46.43
20	50.22	76.44	54.83
25	66.99	80.62	61.32

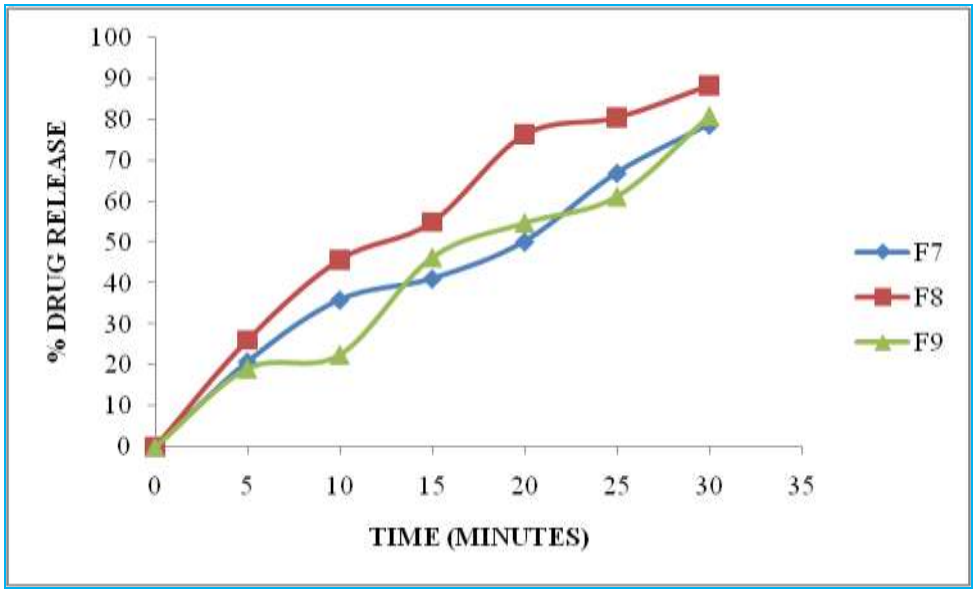

Fig6 :*In vitro* dissolution data for formulations F7– F9 .

Among all the formulations F2 formulation containing, Drug and β cyclodextrin in the ratio of 1:2 showed good result that is 97.06 % in 20 minutes, the concentration of superdisintegrants is 30 mg. As the concentration of polymer increases the drug release was decreased. Hence from the dissolution data it was evident that F2 formulation is the better formulation. The formulation is following zero order release kinetics.

CONCLUSION

Zolpidem Tartrate belongs to class II drugs, that is, characterized by low solubility and high permeability therefore, the enhancement of its solubility and dissolution profile is expected to significantly improve its bioavailability and reduce its side effects. The standard curve of Zolpidem Tartrate was obtained and good correlation was obtained with R^2 value 0f 0.999.the medium selected was pH 6.8 phosphate buffer. Zolpidem Tartrate was mixed with various proportions of excipients showed no colour change at the end of two months, proving no drug-excipient interactions. The precompression blend of Zolpidem Tartrate soild dispersions Immediate release tablets by using super disintegrants were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** The precompression blend of all the batches indicating good to fair flowability and compressibility.

Solid dispersions were prepared with various concentrations of carriers, the prepared solid dispersions were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. Among all the formulations F2 formulation containing, Drug and β cyclodextrin in the ratio of 1:2 showed good result that is 97.06 % in 20 minutes. Hence from the dissolution data it was evident that F2 formulation is the better formulation.

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