Research Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

PROCESS DEVELOPMENT AND OPTIMIZATION FOR MOISTURE ACTIVATED DRY GRANULATION METHOD FOR ZOLPIDEM TARTRATE TABLETS

K. Mary Swarna Latha[*1], B. Sowjanya[1], K. Abbulu[1], E. Pushpa latha[2]

[1*]Department of Pharmaceutics, CMR College of Pharmacy, Medchal, Hyderabad-501401, India.
[2]Department of Pharmaceutical Analysis, CMR College of Pharmacy, Medchal, Hyderabad-501401, India.

ABSTRACT

Moisture activated dry granulation technique is the novel method which increases the commercial aspects and Zolpidem tartrate. The selected drug candidate belongs to the category of Sedative and hypnotic and used for the treatment of insomnia. The aim of the present study was to design Zolpidem tartrate tablets by moisture activated dry granulation technique. Zolpidem tartrate tablets were prepared by using Lactose monohydrate as diluent, microcrystalline cellulose as moisture absorbing agent and magnesium stearate as lubricant. The granules prepared by varying the concentration (1%, 2%, 4%, 6%, 7% 10%) of water and granules were subjected for pre formulation studies (angle of repose, bulk density, tapped density, particle size distribution, compressible index and Hausner's ratio). The prepared granules were subjected for compression and the tablets were subjected for post formulation studies (thickness, weight variation, hardness, friability, disintegration, drug content, dissolution study). The Zolpidem tartrate tablets release profile was carried by using water as the dissolution medium. The prepared granules and tablets are compared to the Zolpidem tartrate granules and tablets prepared by using wet granulation technique (10% concentration of water). Among all the formulations 5% concentration of water is concluded as best formulation by comparing with wet granulated formulation.

KEYWORDS

Zolpidem tartrate tablets, Granulation techniques, MADG and Novel granulation technique.

Author for Correspondence:

Mary Swarna Latha K,
Department of Pharmaceutics,
CMR college of Pharmacy, Hyderabad, India.

Email: maryswarnalathakelam@gmail.com

INTRODUCTON

Tablets are solid, unit dosage forms. It can be defined as solid, flat or biconcave disc prepared by compressing a drug or mixture of drugs with or without suitable diluents. About 90% of drugs are available in the form of tablets to produce therapeutic effect[1].

Compressed tablets are prepared by drying and granulating the material. Granulation method can be

broadly classified into three types: Wet granulation, Dry granulation, and Dry Granulation incorporating bound moisture[2].

MADG is a process in which moisture is used to activate granule formation, without the need to apply heat to dry the granules[3]. There are two main stages in MADG:

Agglomeration

Moisture distribution/ Absorption

During agglomeration, drug is blended with diluents and binder in the powder form, to obtain a uniform mixture[4]. This blend constitutes approximately 50-80% of formula weight. A small amount of water (1-4%) is sprayed as small droplets onto the powder blend while mixing which moistens the binder and makes it tacky. The binder helps in binding of the drug and non drug substances as they move in a circular motion enforced by the mixing blades. When it is compared to other conventional wet granulation techniques the amount of water used in this process is very small hence does not results in larger lumps formation. The particle size of the agglomerates generally falls in the range of 150-500μm[5].

Moisture absorbents such as microcrystalline cellulose or silicon dioxide, are added as the mixing continues in moisture distribution/absorption stage of MADG Process. The moisture absorbents pick up moisture from the moist agglomerates when they come into contact, resulting in moisture redistribution within the mixture[6]. When this happens, the entire mixture becomes relatively dry. When some of the moisture is removed from the wet agglomerates, some usually the larger particles may break up and some of these agglomerates remain almost unbroken. This process results in granulation with more uniform particle size distribution[7]. Advantages of MADG includes applicablity to more than 90% of the granulation need for pharmaceutical, food and nutritional industry, Time efficient, requires few variables and less energy. MADG is not suitable for moisture sensitive, moisture absorbing APIs and formulations with high drug loading capacity[8,9].

The present work is to carry out the process development and optimization of moisture activated dry granulation on Zolpidem tartrate tablets. Zolpidem tartrate is a sedative or hypnotic agent belongs to the group of newer non-benzodiazepine hypnotics used for the treatment of insomnia. Zolpidem modulates the alpha-subunit, known as the benzodiazepine receptor, within the $GABA_A$ receptor chloride channel macromolecular complex. Zolpidem is rapidly absorbed from the GI tract. Zolpidem modulates the alpha-subunit, known as the benzodiazepine receptor, within the $GABA_A$ receptor chloride channel macromolecular complex. Zolpidem is converted to inactive metabolites in the liver which are eliminated primarily by renal excretion. Half-life of Zolpidem is 2.5hours[10].

MATERIAL AND METHODS

Zolpidem Tartrate was received as a gift sample from Aurobindo Pharma, Hyderabad. Lactose monohydrate was obtained from DMV international. Microcrystalline Cellulose JP from FMC bio polymers, Lactose monohydrate, Sodium starch glycolate from DMV international, Magnesium Stearate JP from Peter greven.

Preparation of granules

Compression of granules into tablets

After granulation the lubricated blend was compressed into tablets by using 8 station mini tablet press GMP machine with required punches and compression parameters.

Pre-formulation studies

The first step in the development of dosage forms is the pre-formulation testing which is defined as physical and chemical properties investigation of a drug product. Information about the stability and bioavailability of the dosage forms is the primary requisite of pre-formulation studies.

Drug-excipients compatibility studies

Excipients were integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage forms depends on the selection of excipients, which are added to facilitate administration of the drug and protect it from degradation.

FT- IR Studies

FT- IR spectroscopy was employed to ascertain the compatibility between Zolpidem Tartrate and the selected excipients. FT-IR studies were carried out for API and excipients. API and the excipients were heated to 105^{o}C for one hour to remove the moisture content if present in a hot air oven. Then in presence of IR lamp, potassium bromide was mixed with drug and/or excipient in 10:1 ratio. Grinding in smooth mortar can effect mixing. The mixtures were then placed in the sample holder of the instrument and the spectra were taken. The spectra were run from 4000 cm^{-1} to 500 cm^{-1} wave number. FTIR spectrum of Zolpidem Tartrate was compared with FT-IR spectra Zolpidem Tartrate with excipients. Disappearance of Zolpidem Tartrate peaks or shifting of peak in any of the spectra was studied.

Physical Properties[14]

The powder of excipients and drugs were characterized by angle of repose, bulk density, tapped density, % compressibility, and Hausner's ratio. The flow properties of powders have a great impact on tableting because non-uniform flow will result in variation in weight of the tablets and creates hardness problem.

Post formulation studies

Evaluation of Zolpidem Tartrate Tablets[15]

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, dimensions (diameter and thickness), weight Uniformity test, hardness, friability, drug content, in- vitro drug release.

Appearance, Shape and Color of tab

The shape of the tablet and color was observed by keeping them in light and under lens. The tablets were checked for presence of cracks, depressions, pinholes etc. if any, uniformity of the color, and the polish of the tablet.

Thickness

The thickness for three tablets (random pick) were measured using digimatic calipers (Mitutoyo Campbell Electronics, Japan) individually in mm and standard deviation was calculated.

Hardness test

The hardness of the three tablets (random pick) were determined using Monsanto hardness tester. The mean and standard deviation values were calculated.

Friability Test

In the Roche friabilator (Electro lab, Mumbai), ten tablets were exposed to rolling, resulting free fall of tablets (6 inches within the chamber of the friabilator) at 25 rpm. The intact tablets were weighed after 4minutes and % friability was calculated.

Drug content

It was determined for 10 tablets from each batch. The prior calculated average weight for 10 tablets was powdered using mortar and pestle and 25mg equivalent to Zolpidem Tartrate in tablet triturate was accurately weighed and transferred to 100ml volumetric flask, made upto the volume was with 0.1NHCl and sonicated (Bandelin Electronics, Berlin) for 15 minutes. Subsequently stock solution was filtered and 5ml filtrate was diluted suitably in 50ml volumetric flask with 0.1NHCl. The assay was carried out at 234nm using UV-visible double beam spectrophotometer (Shimadzu UV-1800, Japan) against 0.1NHCl as blank.

Weight Variation Test

Individually tablets (twenty in number) were weighed and Average weight was calculated and is then compared with the individual tablet weight. The percentage deviation should be within the permissible limits (±7.5%).

***In-vitro* Disintegration Test**

One tablet as placed in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 1.2 maintained at 370 ± 20^{o}C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 1.2 maintained at 370 ± 20^{o}C. Complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds and recorded.

***In-Vitro* Drug Release**

In-vitro drug release of the samples was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900ml of 0.1N HCl

solution, was placed into the dissolution flask maintaining the temperature of 37 ± 0.5°C and rpm of 50. One Zolpidem Tartrate tablet placed in each flask of dissolution apparatus. The apparatus was allowed to run for 60min. 5ml of the sample was pipetted out at predetermined time interval. Samples were filtered through 10µm filters. The fresh dissolution medium was replaced every time with the same quantity of the sample. The collected samples were analyzed at 234nm using dissolution medium as blank. The cumulative percentage drug release was calculated. Drug release, Cumulative percentage drug release, Cumulative percentage drug retained and Model fitting of the release profiles using different models were determined through in-vitro dissolution rate.

RESULTS AND DISCUSSION

Drug-excipients compatibility studies

Compatibility studies were performed using IR interpretation for pure drug and for pure drug and excipients physical mixture and it were found that there were no interactions between the pure drug and the excipients so the further formulation was carried out.

Evaluation of Tablets

Pre compression Parameters

Pre compression parameters such as bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio which are evaluated for prepared tablets and the results are shown in the Table No.4. All formulations showed the angle of repose within 300. The values were found to be in the range of 25.22 ± 0.598 to 30.17 ± 0.633. The loose bulk density and tapped bulk density for all the formulations varied from 0.56 ± 0.014gm/cm3 to 0.62 ± 0.012gm/cm3 and 0.67 ± 0.008gm/cm3 to 0.73 ± 0.018gm/cm3 respectively.

The values obtained lies within the limits and not large differences found between loose bulk density and tapped bulk density. The percent compressibility lies within the range of 13.432 ± 1.978 to 17.808 ± 1.297. All formulations are showing good compressibility. Hausner's ratio of the prepared blends/granules fall in the range of 1.154 ± 0.012-1.289 ± 0.029 indicated that the blends/granules have the required flow property and strength for compression.

Post-compression Parameter

The results of post compression studies such as color, thickness, hardness, friability, weight variation, disintegration, drug content and % cumulative drug release for formulated tablets were tabulated in Table No.5. Tablets showed flat, oval shape in white color. Tablets mean thickness in all the formulations were found to be in the range of 2.45mm-2.60mm. All the results are found to be within the limits (2.60mm to 2.71mm). The results showed that the hardness of the tablets was in the range of 4.6 ± 0.3 to 7.6 ± 0.4KP. Hardness of all the formulations are found to be within the limits except the F-1 and F2 which shown the low hardness because of the less moisture. The results showed that the friability of the tablets was in the range of 0.352% to 0.622%. The friability was found to be within the limits except F-1, F-2 and F-3 which are showing the values out of limits due to less binding activity. Weight of the tablet is 60 mg; so the permissible limit is ±7.5%. The content uniformity of all the formulations was found to be in the range of 97.3 ± 1.6% to 98.5 ± 0.6% which showed that there was uniform distribution of the drug throughout the batch. The IP standard says that Zolpidem Tartrate tablets must contain not less than 95.0% and not more than 105.0% of the stated amount of Zolpidem Tartrate. Thus all the formulations of Zolpidem Tartrate complies with IP limit for assay. The disintegration time of prepared tablets were in the range of 7-9 minutes. All the results are within the pharmacopeial limits.

In- vitro dissolution profile of the formulations

The tablets were evaluated for in vitro dissolution studies in 0.1N HCl buffer of pH-1.2 and the results were shown in the Table No.6. Graph is plotted and is shown in Figure No.11. Among all the 6 formulations prepared by MADG process the F-4formulation shows the highest dissolution rate and drug release. The results shows that the drug release pattern of F-4 and F-6 (WG) are similar.

Table No.1: Unit formula and quantitative details for Zolpidem tartrate 60mg

S.No	Ingredients	Unit formula (mg)	% Content
1	Zolpidem tartrate	5.00	8.33
2	Lactose monohydrate	43.80	73
3	Sodium starch glycolate	0.60	1
4	Purified Water	qs	Qs
5	Microcrystalline cellulose (AvicelPH101)	10.00	16.6
6	Magnesium Stearate	0.60	1
Tablet Weight		60	100

Table No.2: Formulations of Zolpidem Tartrate

S.No	Ingredients (mg)	Formulation Code					
		F1	F2	F3	F4	F5	WG
1	Zolpidem Tartrate	20	20	20	20	20	20
2	Microcrystalline cellulose (Avicel PH101)	8.64	8.64	8.64	8.64	8.64	8.64
3	Lactose Monohydrate	15.4	14.8	13.6	12.4	11.8	10
4	Purified water	0.6 (1%)	1.2 (2%)	2.4 (4%)	3.6 (6%)	4.2 (7%)	6 (10%)
5	Sodium starch glycolate	6	6	6	6	6	6
6	Magnesium Stearate	0.36	0.36	0.36	0.36	0.36	0.36
7	Hydroxy propyl cellulose	3	3	3	3	3	3
8	Microcrystalline cellulose (Avicel PH200)	6	6	6	6	6	6
9	Total tablet weight	60	60	60	60	60	60

Brief manufacturing process of Zolpidem Tartrate granules by MADG

S.No	Process	Description
1	Sifting	Zolpidem Tartrate is passed through 600µm sieve (#30), lactose monohydrate sifted through 425 µm sieve (# 40).
2	Dry Mixing	Load the material (except MCC) into Rapid mixing granulator (RMG) and mix for 10 min with impeller slow
3	Granulation 3.1 Agglomeration	Water Sprayed into the RMG over a period of 2 min containing dry mix. Check for the granules formation
	3.2. Moisture absorption and Distribution Phase	Remaining quantity of the ingredients are added to the above step and mixed for 2 minutes.
4	Extra granular material sifting	MCC sifted through through 600µm sieve (#30), Magnesium stearate sifted through 425µm sieve (#40).
5	Prelubrication	Sifted MCC except Magnesium stearate added to the agglomerated blend with I/S for 2min.
6	Lubrication	Sifted Magnesium Stearate added and lubricated for 1 min.

Table No.3: Avg. weight of tablet and % deviation allowed

S.No	Average weight of a tablet	Percentage deviation
1	130 mg or less	10%
2	More than 130 mg and less than 324 mg	7.5%
3	324 mg or more	5%

Table No.4: Pre compression Parameters for the granules

Formulation code	Angle of respose	Loose bulk density(gm/cm^3)	Tapped density(gm/cm^3)	% compressibility	Hausner's Ratio
F1	29.23±0.173	0.57±0.018	0.70±0.008	13.436±1.978	1.235±0.021
F2	25.22±0.598	0.58±0.005	0.68±0.016	14.625±1.043	1.289±0.029
F3	27.31±0.643	0.62±0.007	0.67±0.008	15.492±1.784	1.130±0.012
F4	26.37±0.545	0.59±0.005	0.71±0.007	16.205±1.261	1.164.±0.014
F5	28.22±0.449	0.56±0.004	0.69±0.023	15.666±1.120	1.144±0.015
F6(WG)	26.17±0.633	0.60±0.018	0.72±0.018	16.808±1.297	1.154±0.012

Table No.5: Post-compression Parameters for the developed formulation

Formulation code	Physical appearance	Thickness (mm)	Hardness(Kg)	Friability (%)	Wt. Variation (mg)	Drug Content (%)	*In-Vitro* disintegration time(min)
F1	Clear, white	2.59±2.72	4.05±.3	0.20%	60.8±1.34	91.5±1.0	7.2±0.3
F2	Clear, white	2.58±2.65	4.1±5.0	0.43%	59.75±1.1	92.3±1.6	7.3±0.8
F3	Clear, white	2.59±2.70	3.3±4.6	0.45%	60.81±1.3	93.6±1.1	7.3±0.6
F4	Clear, white	2.60±2.65	7.2±0.4	0.38%	70.55±1.5	97.1±1.3	7.9±0.5
F5	Clear, white	2.59±2.70	5.3±4.6	0.41%	60.55±1.3	92.5±0.6	7.1±0.5

Table No.6: *In vitro* drug release profile for prepared formulations

S.No	Time (min)	Cumulative % drug released					
		F1	F2	F3	F4	F5	WG
1	0	0	0	0	0	0	0
2	5	28.161±1.21	29.732±1.09	32.517±1.32	44.588±0.35	35.945±1.07 4	45.371±1.43
3	10	45.011±1.13	42.887±0.76	40.588±1.14	58.402±0.94	43.761±1.14	58.868±1.24
4	20	52.372±0.98	54.122±0.98	52.325±1.08	65.365±0.65	53.726±1.17	62.854±0.97
5	30	55.854±1.12	57.854±1.12	57.854±1.12	72.943±0.71	65.365±0.65	71.481±0.76
6	40	62.365±1.23	65.118±0.79	62.854±0.97	80.308±1.53	74.028±1.65	78.003±0.43
7	50	78.298±1.34	84.484±0.97	72.943±0.71	90.043±0.58	79.767±0.96	89.593±0.98
8	60	90.130±1.10	91.899±1.23	88.224±0.95	98.115±0.64	90.772±0.87	95.136±0.78

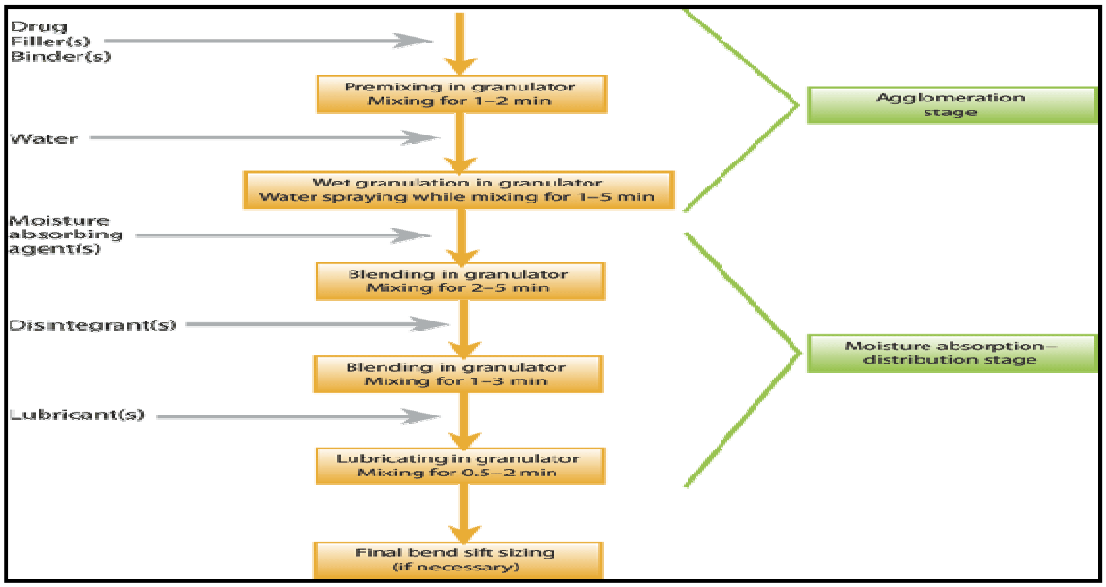

Figure No.1: Flow diagram of the moisture-activated dry-granulation process

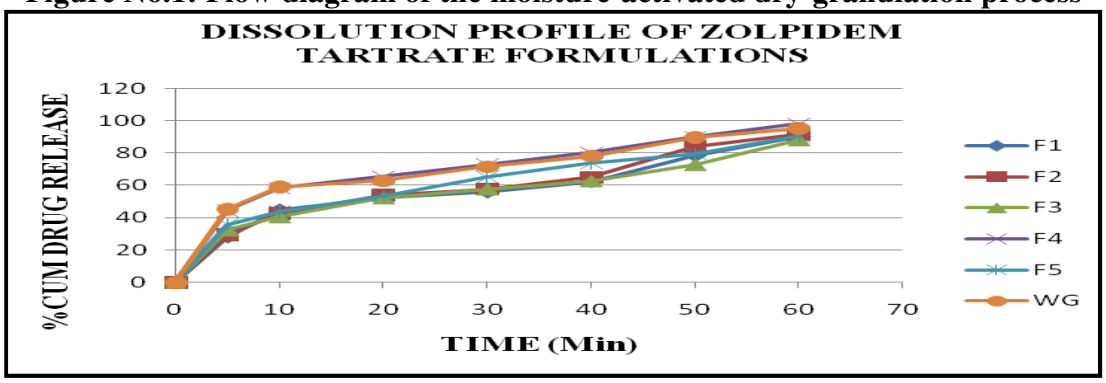

Figure No.2: Dissolution Profile of Zolpidem Tartrate Formulations

CONCLUSION

The study was undertaken with an aim to develop an optimized formulation of Sedative and hypnotic agent, Zolpidem tartrate by oral drug delivery. The active pharmaceutical ingredient, Zolpidem tartrate was selected and formulated as orally immediate release tablets of 60 mg, comparable to the Reference product. In the present work, FTIR studies were done to know the drug excipients compatibilities. Suitable excipients were selected for formulation development based on the FTIR results. Tablets were prepared by using Moisture activated dry granulation technique. During development of formula, various in process tests such as bulk density, tapped density, Hausners ratio, compressibility index were evaluated and weight variation, hardness, thickness, disintegration time were evaluated for core tablets. Finished products were evaluated for disintegration time, and *In-vitro* release studies. The developed trials were tested for *In-vitro* dissolution profile and compared with the marketed product. The *In-vitro* dissolution profile of formulation F4 was similar to that of WG (F6). The optimized batch tablets were packed in HDPE containers and stability studies was performed at 25ºC ± 2ºC/ 60% ± 5%RH. Stability samples were evaluated initially and after one and two months. The results were compared with the predetermined specifications. All the results were found to be satisfactory. Hence the designed and developed formula of Zolpidem tartrate was stable. The objective of the present project was successfully achieved by developing the product of similar drug release profile to that of Reference product.

ACKNOWLEDGEMENT

The authors are sincerely thanks to the Department of Pharmaceutics, CMR College of Pharmacy, Medchal, Hyderabad-501401, India for providing the facilities to complete this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBILIOGRAPHY

1. Lachman L, Liberman H and Kanig J. The Theory of practice of Industrial pharmacy, *Published by Lea and Febiger,* 3rd Edition, 1986, 293-345, 346-373.
2. Herbert A, Joseph L. Leon Lachman, Liberman, Kanig. The Theory and Practice of Industrial Pharmacy, *Varghese Publishing House, Bombay,* 3rd Edition, 1986, 320-321.
3. Ismat U, Jennifer W. Moisture-Activated S-YC, Granulation-Part I, Gary J W, Nemichand B J, *et al.* A guide to excipient and equipment selection and formulation development, *Pharm Tech,* 33(11), 2009, 62-70.
4. Ismat U, Jennifer W, Shih Y C, Hang G, San K, Nemichand B J. Moisture-activated dry granulation part II: the effects of formulation ingredients and manufacturing-process variables on granulation quality attributes, *Pharm Tech,* 33(12), 2009, 42-51.
5. Susan F, Carrie S, Brian J, Shawn E, Ismat U. Optimization of binder level in moisture activated dry granulation using absorbent starch to distribute moisture, Available from www.vectorcorporation.com/newspapersasp May 1426, 2011, 19.
6. Aniruddha M R, Joseph B S. Use of a moist granulation technique to develop controlled-release dosage forms of acetaminophen, *Drug DevInd Pharm,* 27(4), 2001, 337-343.
7. Christensen L H, Johansen H E, Schaefer T. Moisture-activated dry granulation in a high shear mixer, *Drug DevInd Pharm,* 20(14), 2009, 2195-2213.
8. Aniruddha M R, Joseph B S. Evaluation and comparison of a moist granulation technique to conventional methods, *Drug DevInd Pharm,* 26(8), 2000, 885-889.
9. Aniruddha M R, Joseph B S. The effects of formulation factors on the moist granulation technique for controlled-release tablets, *Drug DevInd Pharm,* 27(9), 2001, 893-898.
10. Tripathi K D. Essentials of medical pharmacology, *Jaypee Brothers Medical Publisher,* 6th Edition, 2008, 388-389.

Please cite this article in press as: Mary Swarna Latha K *et al.* Process development and optimization for moisture activated dry granulation method for Zolpidem tartrate tablets, *Asian Journal of Research in Chemistry and Pharmaceutical Sciences,* 7(3), 2019, 892-899.