Research Journal of
Pharmacology

Development of Low Dose Eszopiclone Drug Formulation by Using Geometric Blending Method

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Key words: Geometric blending, low-dose active ingredients, homogeneous distribution, Eszopiclone, insomnia

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Page No.: 44-48
Volume: 14, Issue 4, 2020
ISSN: 1815-9362
Research Journal of Pharmacology

Abstract: Eszopiclone is a type of medicine used in the treatment of insomnia with a hypnotic effect. The aim of this study is to create Eszopiclone 3 mg tablet formulation by providing homogeneous distribution of Eszopiclone raw material which is found in low amount in the drug, into the Excipients. In order to achieve homogeneous blending, 4 trial production and pilot studies were carried out using the geometric blending and elimination method. Trial 4 was optimized and the process validation study was approved. Acceptable content uniformity values of trial 4 and pilot study were calculated as 8.63 and 8.74%, respectively. In this study, the importance of geometric blending and elimination method is shown.

INTRODUCTION

The non-benzodiazepine hypnotic agent Eszopiclone has been available in Europe, since, 1992 and in the USA, since, 2005[1]. Eszopiclone is used to relieve problems such as insomnia and falling asleep by binding to the central nervous system. Eszopiclone, causes the chloride channels to open and so that, the inhibitory effect of GABA (gamma-aminobutyric acid-benzodiazepine) increases[2]. This situation causes sleep as it provides a hypotenic effect. The formulation was created using low dose eszopiclone to regulate the sleep problem. The geometric replication method was used because the active ingredient dosage would be difficult to distribute in the fillers due to its low dosage. Thus, a homogeneous distribution was achieved (Fig. 1).

Eszopiclone molecule is defined as a white or light-yellow crystalline powder. Its physical properties are; non-hygroscopic, soluble in phosphate buffer, slightly soluble in water and slightly soluble in ethanol. It has a melting point of 202°C and a boiling point of 487.2°C.

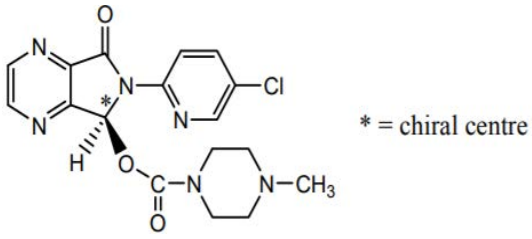

Fig. 1: The molecular structure of Eszopiclone[3]

The 3, 2 and 1 mg tablets available in the market are defined as Lunesta[4]. The Excipients used; Calcium Phosphate, Microcrystalline Cellulose, Croscarmellose Sodium, Lactose, Colloidal Silicon Dioxide, Magnesium Stearate, Opadry Blue.

Eszopiclone 3 mg coated tablet has been accepted according to European guidelines. The selection of auxiliary substances used in tablet production is determined according to the production method. The Biopharmaceutical Classification System (BCS) of the

Eszopiclone drug is defined as class II[5]. For this reason, it is very important to homogeneously distribute Eszopiclone to the excipients. The formulation was developed as a tablet coated with drug release similar to the reference product named Lunesta[6].

Homogeneous distribution is very important in the production of low dose oral drugs. The homogeneity of the active ingredients plays a key role in the direct compression method as it will affect the dissolution, absorption and bioavailability of the drugs. In order to ensure the homogeneity of the mixture, attention should be paid to the size of the equipment used for mixing, the sieve size to be used in the sieving process, the raw material particle sizes and the raw material moisture levels.

We have outlined the Eszopiclone 3 mg Film-Coated Tablet formulation by direct compression of the geometric dilution method. We demonstrated the blending technique by distributing low doses of Eszopiclone to excipients in medicine.

MATERIALS AND METHODS

Materials: Eszopiclone active substance was procured by (Centaur, India). The excipient which are used as respectively; Calcium Phosphate (JRS Pharma, India), Microcrystalline Cellulose (FMC, Ireland), Croscarmellose Sodium (FMC, Ireland), Lactose (Kerry, Norway), Aerosil 200 (Evonik, Germany) and Magnesium Stearate (Peter Greven, Germany) supplied. All excipients used are suitable for direct compression method and geometric blending.

Method: Trial studies indicated in Table 1 were performed using the homogeneous blending method. In addition, all tablet formulation theoretically was contained 3 mg of active substance.

To be able to perform the tablet compression process in the formulas created, the powder flow must be good. In the theoretical calculation of the powder flow, after calculating the bulk density (ρ_{bulk}) and tapped density (ρ_{tap}) parameters, the Compressibility Index (CI) and the Hausner Ratio (HR) are calculated to see how good of the powder flow is.

Bulk density measurement is measured by filling powder into a 100 mL measuring tape. The bulk density (ρ_{bulk}) is calculated by dividing the weight of the powder (g) by its bulk volume (V_0). Bulk density: $\rho_{bulk} = g/V_0$.

By tapping on a compacted density powder cluster, fine particles are placed in the spaces between the larger particles and the volume of the powder is measured. The volume of the powder decreases in proportion to the number of hits. When the interparticle spaces are completely filled, the decreasing on the volume reaches a certain point and stops. The tapped density (ρ_{tap}) is calculated by dividing the weight of the powder (g) by the tapped volume (V_t). Tapped density = $\rho_{tap} = g/V_t$. The flowing character from bulk density to tapped density is observed by two steps: Compressibility index (Carr's index):

$$CI = \frac{\rho_{tap} - \rho_{bulk}}{\rho_{tap}} * 100$$

Hausner Ratio (HR):

$$HR = \frac{\rho_{tap}}{\rho_{bulk}}$$

- Bulk density (ρ_{bulk}): 0.416 (g/mL)
- Tapped density ($\rho_{tap.}$): 0.477 (g/mL)
- Carr's index: (0.477-0.416)/0.477*100 = 12,79%
- Hausner Ratio (HR): 0.477/0.416 = 1.15

According to the CI and HR results calculated with the bulk density and tap density information as shown in Table 2, the powder flow is in the excellent flowing character. This excellent powder flow provides information on tablet compressibility.

Lab-scale studies: Direct compression was carried out by providing the distribution of the active ingredient in the formulation in small amounts with the geometric blending method. Trials 1-4 were conducted with 750 g powder. The pilot study was conducted with 3 kg of powder.

Trial 1: Eszopiclone, Calcium Phosphate, Microcrystalline Cellulose, Croscarmellose Sodium and Lactose Anhydrous through the sieve 0.6 mm into

Table 1: Formulation of Eszopiclone 3 mg Tablet

Ingredients	Function	Trial 1	Trial 2	Trial 3	Trial 4	Pilot study
Eszopiclone	Active substance	3 mg	3 mg	3 mg	3 mg	3 mg
Calcium Phosphate	Dispersive	-	-	-	-	-
Microcrystalline Cellulose	Filler	-	-	-	-	-
Croscarmellose Sodium	Filler	-	-	-	-	-
Lactose Anhydrous	Diluent	-	-	-	-	-
Colloidal Silicon Dioxide	Glidant	-	-	-	-	-
Magnesium Stearate	Lubricant	-	-	-	-	-

Table 2: Flowing character according to Carr's index and Hausner's ratio

Flowing character	Carr's index'i (%)	Hausner ratio
Excellent	5-15	1.05-1.18
Good	12-16	1.14-1.19
Appropriate	18-21	1.22-1.27
Weak	23-35	1.30-1.54
Too weak	33-38	1.49-1.61
Too weak	>40	>1.67

container and mixed for 10 min. Colloidal Silicon Dioxide through sieve 0.6 mm add onto the powder and mixed for 5 min. Magnesium stearate through the sieve 0.5 mm, add onto the powder and mixed for 3 min. Mixtures were provided in a cubic mixer. Compress obtained powder mixture in tablet compressing machine with specified punches in compliance with its specifications.

Trial 2: Eszopiclone and Calcium phosphate through the sieve 0.6 mm into container and mixed for 10 min. Microcrystalline Cellulose through the sieve 0.6 mm add onto the powder and mixed for 10 min. Croscarmellose Sodium through the sieve 0.6 mm add onto the powder and mixed 10 min. Lactose Anhydrous through the sieve 0.6 mm add onto powder and mixed 10 min. Colloidal Silicon Dioxide through the sieve 0.6 mm add onto powder and mixed 5 min. Magnesium stearate through the sieve 0.5 mm, add onto the powder and mixed for 3 min. Mixtures were provided in a cubic mixer. Compress obtained powder mixture in tablet compressing machine with specified punches in compliance with its specifications.

Trial 3: Eszopiclone and Calcium Phosphate were mixed and sieved through a 0.6 mm sieve. Then, microcrystalline cellulose was added to the sieved mixture by geometric mixing method and sieved through a 0.6 mm sieve again and the cubic mixture was mixed at 60 rpm for 10 min to ensure a homogeneous mixture. Croscarmellose Sodium through the sieve 0.6 mm add onto the powder and mixed at 60 rpm for 10 min. Lactose Anhydrous through the sieve 0.6 mm add onto the powder and mixed 60 rpm for 10 min. Colloidal Silicon Dioxide through the sieve 0.6 mm add onto the powder and mixed at 60 rpm for 5 min. Magnesium stearate through the sieve 0.5 mm, add onto the powder and mixed for 3 min. Mixtures were provided in a cubic mixer. Compress obtained powder mixture in tablet compressing machine with specified punches in compliance with its specifications.

Trial 4: The mixture of eszopiclone and Calcium phosphate, sieved through a 0.4 mm sieve was mixed at 60 rpm for 10 min. Anhydrous Lactose, sieved through a 0.6 mm sieve is added to the powder and mixed at 60 rpm for 10 min. Microcrystalline cellulose sieved through a 0.6 mm sieve was added to the powder mixture by geometric mixing method. Each step was performed at 60 rpm for 10 min. Colloidal Silicon Dioxide and Microcrystalline Cellulose are blended and sieved through a 0.6 mm sieve, added to the powder and mixed for 5 min at 60 rpm. Magnesium Stearate, sieved through 0.5 mm sieve, is added to the powder mixture and mixed at 60 rpm for 3 min. Mixtures were provided in a cubic mixer. Compress the powder mixture obtained in the tablet compression machine with the specified punches in accordance with its specifications (Fig. 2).

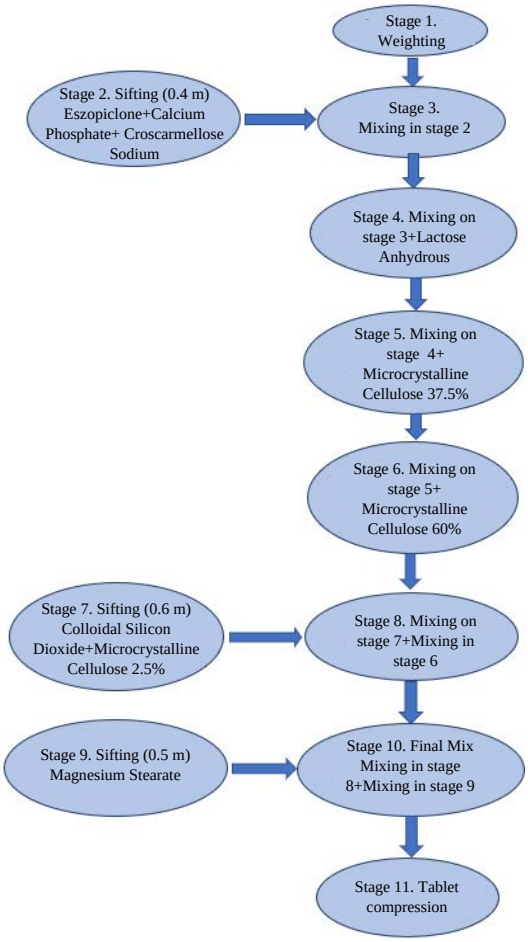

Fig. 2. Flow diagram for trial 4

Pilot study: Pilot production is similar to trial 4. Pilot production lot size is 3 kg. Production Method; The mixture of eszopiclone and Calcium phosphate, sieved through a 0.4 mm sieve, was mixed at 60 rpm for 10 min. Anhydrous Lactose, sieved through a 0.6 mm sieve, is added to the powder and mixed at 60 rpm for 10 min. Microcrystalline cellulose sieved through a 0.6 mm sieve was added to the powder mixture by geometric mixing method. Each step was performed at 60 rpm for 10 min.

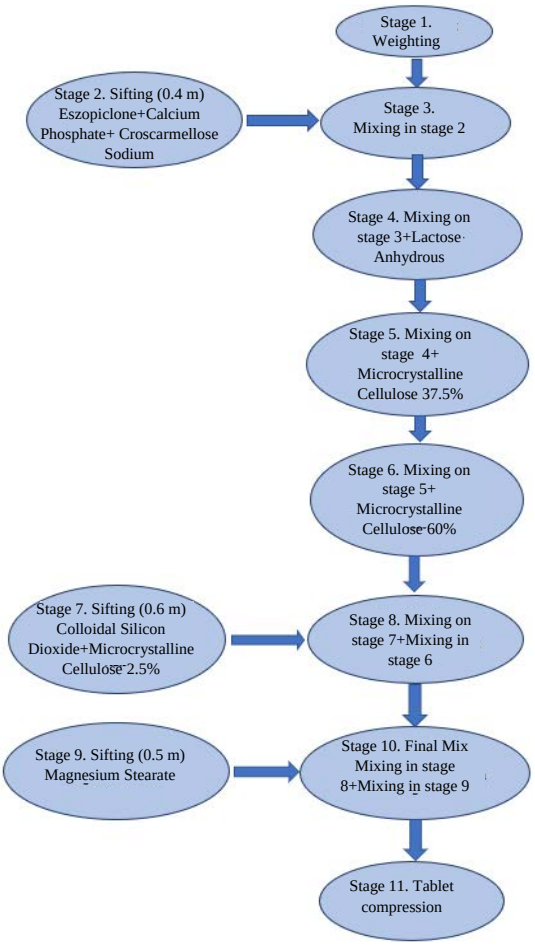

Fig. 3: Flow diagram for plot study

Table 3: Accepted Value (AV) calculation conditions[7]

Conditions	----------Values----------	
If 98.5%<X<101.5, then	M = X	AV = ks
If X<98.5%, then	M = 98.5%	AV = 98.5-X+ks
If X>101.5, then	M = 101.5%	AV = X-101.5+ks

X = Average; k = 2.4; S = Standard Deviation

Collaidal Silicon Dioxide and Microcrystalline Cellulose are blended and sieved through a 0.6 mm sieve, added to the powder and mixed for 5 min at 60 rpm. Magnesium Stearate, sieved through 0.5 mm sieve, is added to the powder mixture and mixed at 60 rpm for 3 min. Mixtures were provided in a cubic mixer. Compress the powder mixture obtained in the tablet compression machine with the specified punches in accordance with its specifications. The production stage is shown in Fig. 3 in detail.

Accepted value (AV) calculation for pilot study and trial studies (Table 3): Pharmacopeia limit (HPLC Eur. Ph. 2.2.29 and Eur. Ph. 2.9.40) is that Acceptance value of 10 units is less than or equal to 15.0%[7].

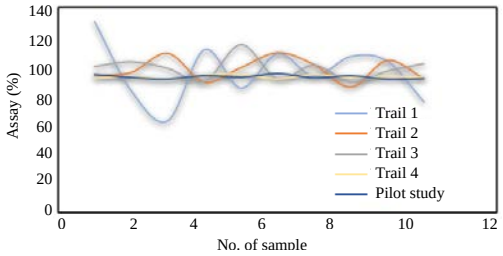

Fig. 4: Content uniformity results vs. sample of each Eszopiclone 3 mg Tablet

Table 4: Content uniformity results of Eszopiclone 3 mg Tablet

Uniformity of dosage units (Content uniformity) 3 mg	Trial 1	Trial 2	Trial 3	Trial 4	Pilot study
Sample 1	130.00	93.400	99.430	91.63	94.32
Sample 2	83.140	95.310	102.62	93.00	92.35
Sample 3	72.850	108.30	98.100	91.02	91.34
Sample 4	110.85	88.760	89.140	93.86	93.53
Sample 5	85.000	98.600	114.30	94.36	92.50
Sample 6	108.20	108.70	91.000	91.43	94.83
Sample 7	93.000	100.58	100.36	94.20	92.12
Sample 8	106.30	89.200	88.760	92.14	93.41
Sample 9	103.10	103.43	96.240	93.14	91.23
Sample 10	75.450	91.230	101.34	92.35	91.72
Average	95.770	97.370	98.130	92.71	92.73
Standard Deviation	19.740	7.960	7.6100	1.190	1.240
Relative Standard Deviation (RSD)	20.610	8.180	7.7600	1.280	1.340
Accepted Value (AV) (%)	50.110	20.24	18.640	8.630	8.740

RESULTS AND DISCUSSION

The results of trials which's production are completed are given in Table 4. It is suitable to choose the best trial according to the results of content uniformity. Content uniformity is checked with 10 tablets. After the appropriate trial was chosen, pilot production was made and the trial results were shared. The pilot production study was conducted with trial 4 references. The acceptance value of trial results was taken as a reference to the European pharmacopoeia (Fig. 4).

The importance of homogeneous mixing and sieving for dry mixing method can be understandable by considering content uniformity results. With the purpose of achieving homogeneous distribution of the active ingredient especially for the formulations which include small amount of active ingredient such as Eszopiclone amount, geometric blending and sieving method used. In addition, during the trial 4 and scale-up studies, the production was made by paying attention to the mass density in the use of geometric blending technique.

Depending on the bulk density, the minimum filling rate of the tank to be mixed should be 40% and the maximum filling rate should be 80%. With these properties, the mixture will be homogeneous.

CONCLUSION

Eszopiclone is a drug for the treatment of insomnia. Sieving and geometric blending method were used in the studies conducted for the pilot study. The content uniformity results of the trials are given in Table 4. According to the content homogeneity in Table 4, the most appropriate production method is trial 4. The reason why trial 4 is suitable is product development with the use of small sieves and geometric mixing method. The formula, created by the geometric blending method, provides a homogeneous distribution of low-dose raw materials such as Eszopiclone.

By optimizing trial 4, thesuitabilityof a large-scale pilot study, namely the elimination method and the geometric blending method, was observed. As seen in Table 4, the content uniformity results of the pilot production are homogeneous.

The homogeneous dispersion of the active substance at low doses affects the absorption and bioavailability of the drug.If the homogeneous spread of the active substance cannot be reach, the wish dose can't be obtained if the drug is used for curative aim.

ACKNOWLEDGMENT

This work was supported by World Medicine İlaç San. ve Tic. A.Ş.

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