Investigation of Dry Granulation and Wet Granulation Effect on Dissolution Profile of the Developed Film Coated Tablets Containing Eplerenone

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Received: 06 Sep, 2021 | Accepted: 20 Sep, 2021 | Published: 25 Sep, 2021

Abstract

The objective is to observe and improve drug release of Eplerenone which is BCS Class II API by applying dry granulation and wet granulation process. Inspra 50 mg film coated tablets, manufactured by Pfizer, were taken as reference product to compare with dissolution profiles of dry granulation applied product and wet granulation applied product. Investigation of the effect of wet granulation process on dissolution profiles of Eplerenone 50 mg film coated tablets has been demonstrated out in the scope the study. While f2 similarity factor is 44.93 for dry granulation applied product, it is 60.62 for wet granulation applied product when compared to reference product. It comply that dissolution rate of wet granulation applied product is more proper to the specification than dry granulation applied product. The study demonstrates the effect of different granulation process on dissolution rate.

Keywords: Wet granulation; Dry granulation; Dissolution; Eplerenone

Introduction

Eplerenone with the CAS registry number of 107724-20-9 is a Selective Aldosterone Receptor Antagonist (SARA) and used for treatment of the patients with chronic heart failure and high blood pressure caused by resistant hypertension due to elevated aldosterone. The molecular formula and weight of Eplerenone are C24H30O6 and 414.49 respectively [1].

Within the Biopharmaceutics Classification System (BCS), Eplerenone is class-II Active Pharmaceutical Ingredient (API) [2]. It is off-white to white powder which is soluble in Dichloromethane, slightly soluble in Methanol and insoluble in water [1]. The structure of the Eplerenone molecule is shown in below as figure 1. Eplerenone is found as tablet form with 25 mg and 50 mg dosage in the market and supplied from Pfizer as Inspra 25 mg film coated tablets and Inspra 50 mg film coated tablets.

Combination of small particles with the help of mechanical force or a binding agent to form granules is called granulation in the pharmaceutical industry. It is important for improving API’s ultimate utility and controlling the release rate of the active ingredient. The purposes of the granulation can be described as follows; improving the flow characteristic of the mixture, preparing homogeneous mixtures that will not disperse over time and improving compaction [3]. Dry granulation and wet granulation are most common granulation methods for solid dosage forms.

Dry granulation is forming granules without using a liquid solution. The process is applying for products which are sensitive to moisture and heat. It can be done in two ways as slug compression or compactor. Slug compression process is done by pressing and crushing tablets (briquettes) in order to make powder mixtures whose flowability is not suitable for the tablet pressing process to granules. Compactor is the process of obtaining granules by compacting the powder with two rollers, obtaining briquettes in strips and grinding them [4,5].

Wet granulation is forming granules by adding a liquid solution to powder. Solvent that is used in granulation should be volatile, e.g. water, ethanol and isopropanol. The process helps to reduce segregation possibility by binding excipient with API. This method yields better flowability to a formulation. Wet granulation takes advantages of being robust process suitable for most compounds against dry granulation. Low shear granulation, high shear granulation and fluid bed granulation are type of granulation. Selection of the method depends on physicochemical properties of the API and excipients, required flow and release properties [4,5].

Considering the fact that almost 40% of pharmaceuticals in the
Trial 1

Eplerenone, lactose monohydrate, croscarmellose sodium, hypromellose, and avicel PH-102 were sifted with 0.6 mm sieve and mixed in the Qubic mixer at 60 rpm for 15 minutes. Sodium lauryl sulphate was sifted with 0.6 mm sieve and added to the first mixture and mixed for 10 minutes. Talc and Magnesium stearate were sifted with 0.5 mm sieve and added to the second mixture separately and mixed for 3 minutes. Slug compression is applied by compressing, crushing and compressing tablets respectively. The dispersion of Opadry yellow, which is Hydroxypropyl Methyl Cellulose (HPMC) based film coating material, in purified water is prepared for coating process, mixed at 500 rpm for 30 minutes. Core tablets that compressed in accordance with their specifications are coated with Opadry yellow dispersion. Film coating is applied till 10 mg coating is done. Flow diagram of the process is shown in figure 2.

Trial 2

Eplerenone, lactose monohydrate, croscarmellose sodium, microcrystalline cellulose and hypromellose were mixed in the high shear granulator. Sodium lauryl sulphate dissolved in purified water. Granulation is done by adding solution to the mixed powder. Wet granules dried at 45°C in fluid bed dryer. The loss on drying value was checked with Infrared moisture analyzer and is not more than 3%. Dry granules were sifted with 0.8 mm Frewitt sieve. Microcrystalline cellulose added to the dry granules and mixed in Qubic mixer for 10 minutes at 60 rpm. Talc and magnesium stearate, which were sifted

Figure 1: Structure of the Eplerenone molecule [1].

Figure 2: Flow diagram of dry granulation method (SLUG compression process).
Table 1: Formulation of the Eplerenone 50 mg film coated tablets.

| Materials            | Unit Formula* (mg) | Function       | Supplier            |
|----------------------|--------------------|----------------|---------------------|
| **Active Substance** |                    |                |                     |
| Eplerenone           | 50.00              | Active Substance | MSN                 |
| **Excipients**       |                    |                |                     |
| Lactose Monohydrate  | 71.40              | Diluent        | MEGGLE              |
| Sodium Lauryl Sulphate | 1.70             | Surfactant     | HUNSTMAN            |
| Croscarmellose Sodium | 8.50              | Disintegrant   | DUPONT              |
| Hypermellose         | -                  | Binder         | COLORCON            |
| Microcrystalline Cellulose | -          | Filling Agent  | DUPONT              |
| Talc                 | -                  | Lubricant      | LUZENAC             |
| Magnesium Stearate   | -                  | Lubricant      | PETER GREVEN        |
| **Core Tablet Weight** |                  |                |                     |
| Opadry Yellow        | 10.00              | Coating Agent  | COLORCON            |
| Pure water\(^1\)     | -                  | -              | -                   |
| **Film Coated Tablet Weight** | -            |                |                     |

\(^1\)Not found in finished product.  
\(^*\)As a company policy, we cannot share the unit formula.

Figure 3: Flow diagram of wet granulation method.
with 0.5 mm sieve, added to dry granules one by one and mixed for 3 minutes respectively. Core tablets are compressed in accordance with their specifications and coated 10 mg with Opadry yellow dispersion. Flow diagram of the process is shown in figure 3.

**Results and Discussion**

In the scope of the study, dissolution test was applied on both reference product which is Inspra 50 mg film coated tablets and Eplerenone 50 mg film coated tablets which are produced by applying two different methods that are dry granulation and wet granulation.

Chromatographic conditions for dissolution are as given in table 2 according to the European Pharmacopoeia (EP) monograph 2.9.3. The method used for Eplerenone amount determination is based on European Pharmacopoeia (EP) monograph 2.2.25. The instruction is ‘minimum 80% of label claim in 30 minutes’ [14,15].

The results of dissolution rate profiles of reference product and dry granulation applied product and wet granulation applied product are given in the table 3 and table 4, respectively. Besides, comparison of dissolution rate profiles of reference product vs. dry granulation

![Figure 4: Comparison of dissolution rate profiles of reference product vs. dry granulation applied product.](image)

![Figure 5: Comparison of dissolution rate profiles of reference product vs. wet granulation applied product.](image)
Table 2: Chromatographic conditions.

| Used device                  | UV spectrophotometer |
|------------------------------|----------------------|
| Wavelength                   | UV, 245 nm           |
| Dissolution medium           | 0.1 N HCl            |
| Volume of dissolution medium | 1000 ml              |
| Temperature of dissolution medium | 37°C ± 0.5        |
| Stirring speed               | 50 rpm               |
| Apparatus                    | Pedal                |
| Time                         | 30 minutes           |

Table 3: Results of dissolution rate profiles of reference product and dry granulation applied product.

| Time (Minute) | 0  | 5 | 10 | 15 | 20 | 30 |
|---------------|----|---|----|----|----|----|
| Product (%)   |    |   |    |    |    |    |
| Eplerenone 50 mg film coated tablets | 0.0 | 38.96 | 62.62 | 66.41 | 76.02 | 80.85 |
| Reference Product (%) |    |   |    |    |    |    |
| Inspra 50 mg film coated tablets | 0.0 | 29.51 | 67.42 | 84.72 | 91.66 | 96.21 |

Table 4: Results of dissolution rate profiles of reference product and wet granulation applied product.

| Time (Minute) | 0  | 5 | 10 | 15 | 20 | 30 |
|---------------|----|---|----|----|----|----|
| Product (%)   |    |   |    |    |    |    |
| Eplerenone 50 mg film coated tablets | 0.0 | 35.23 | 73.29 | 88.47 | 101.12 | 104.71 |
| Reference Product (%) |    |   |    |    |    |    |
| Inspra 50 mg film coated tablets | 0.0 | 31.16 | 70.17 | 85.59 | 92.51 | 96.54 |

The results should be considered according to specification which is 'minimum 80% of label claim in 30 minutes'. According to results on the table 3, 96.54% of reference product dissolves in 30 minutes. However, 80.85% of dry granulation applied product dissolves in 30 minutes. Even the result comply the specification, it is still not approximate the dissolution rate of reference product which is 96.54%, which is undesired situation. Also, the graph of comparison of dissolution rate profiles of reference product versus dry granulation applied product shows the differences between profiles clearly. It explains that the f2 similarity factor, which is 44.93, is not suitable.

According to the dissolution rate results of the wet granulation applied product as shown in table 4, 104.71% of product dissolves in 30 minutes while 96.54% of reference product dissolves in 30 minutes. With the increasement of the dissolution of tablets of wet granulation applied product, f2 similarity factor, which is 60.62, to reference product is also increased.

**Conclusion**

The effect of the wet granulation process on dissolution profile of Eplerenone 50 mg film coated tablets is investigated by comparing both dissolution rate results of dry granulation and wet granulation. Dissolution rate results of the products were compared with the dissolution rate of the reference product. While dissolution is 80.85 for dry granulation applied product, it is 104.71 for wet granulation applied product within 30 minutes. Similarity factor f2 is 44.93 and 60.62 for dry granulation applied product and wet granulation applied product, respectively. The results demonstrate that drug release of wet granulation applied product occur in more appropriate manner when compared with dry granulation applied product. The study shows that besides the effects of solubility, polymorphic form, particle size, amount in the drug dosage form and surface active agents, different manufacturing process are also have significant effect on dissolution rate.

**Acknowledgement**

The study was supported by World Medicine İlaç San. ve Ticaret A.Ş.

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