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Research Article

# Enhancement in Flowability, Dissolution and Drug Release of Telmisartan through Spherical Crystallization

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**ABSTRACT**

A novel particle manufacturing process called spherical agglomeration can satisfy the requirements for direct compression. Telmisartan is an anti-hypertensive medicament which exhibits poor water solubility as well as flow properties. Spherical agglomerate was prepared by spherical crystallization technique. Dimethyl formamide and Dimethyl Sulfoxide performs as a good solvent, water as anti-solvent for Telmisartan and Dichloromethane, Chloroform and Ethyl Acetate act as binding liquid for agglomeration process. Prepared agglomerate was subjected for micromeritics as well as mechanical properties. Improvement in dissolution behaviour observed in formulation batches as compared to pure Telmisartan. The significant improvement in micromeritics properties observed because of size enlargement and spherical shape it revealed that the change in the crystal habit. A crucial step in creating a Telmisartan spherical agglomeration and a workable strategy for changing the material's characteristics for direct compression is determining the processing parameters.



## INTRODUCTION

One crucial factor in attaining the precise drug concentration in the systemic circulation for therapeutically response is solubility, which is the occurrence of the dissolution of solid in liquid phase to provide a homogeneous system [1]. To achieve a drug solution in GI fluid is crucial prerequisite for weakly water-soluble medication in order for absorption from the GI tract to be possible. Horter and Dressman [2] defined a medicine is considered to be poorly water-soluble if, under normal circumstances, it takes longer for it to dissolve in the GI fluid than it does for it to pass from absorption sites in the gastrointestinal tract. Common drug dissolve methods include salt formation, particle size reduction etc., but due to some practical restrictions with these methods, obtaining target bioavailability augmentation may not always be attainable [3].

Spherical crystallization is described as "a novel particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form". This method's simple and capacity to produce spherical agglomerates in a single step account for its special position in oral medication delivery systems.

The resulting spherical agglomerates can be directly compressible or utilised as capsules. They provide benefits like great flow characteristics, homogeneous size distribution, and repeatable packing and filling. Because of the spheres' large surface area and consistent dispersion throughout the gastrointestinal tract (GIT), the localised toxicity is reduced. Additionally, this even distribution may enhance the drug(s)' bioavailability and absorption. The fact that they have a lower surface area to volume ratio than powder or granules makes them a superior coating substrate. Due to its superior handling and dosing characteristics, spheres exhibit an improvement in their therapeutic capabilities. Because they are less prone to dosage dumping, failure of a few units may not have the same negative effects as failure of a single unit [4].

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The fact that spheres are smallest impacted through the typical gastric emptying time means that drug delivery utilizing them is less susceptible to physiological variables, which is another extremely significant benefit. Spherical crystallization is a method of particle design, and its non-convective process imparts the qualities of high flowability, mechanical strength, and compressibility, as well as improves the particle size and gets rid of several processing processes like granulation, drying, etc. Some medications, such as non-steroidal anti-inflammatory medicines (NSAIDS), which have poor compressibility, flowability, and solubility, as well as medications unsuitable for direct compression, can be crystallised spherically [5-6].

## MATERIAL AND METHODS

### Material

Telmisartan were provided by Swapnroop drugs and Pharmaceuticals, Aurangabad, India. Dichloromethane, Chloroform, Dimethyl formanide and Ethyl Acetate were provided by Loba Chemicals, Mumbai and PVP was provided by Molychem, Mumbai.

### Methods

### Preparation of Spherical Agglomerates

Agglomerates of drug were prepared by spherical crystallization method. 10 mg drug was tended to get dissolved in dichloromethane. Chloroform is added to the solution containing drug and thoroughly mixed. The mixture of drug, dichloromethane and chloroform was added at a rate of 1mL/min to water stirred at a rate of 1000 rpm utilizing magnetic stirrer. Stirring were continuous for a time of 40 minutes after whole addition of mixture. The particles of drug obtained in the water was separated by vacuum filtration and dried at 40°C. A particle was washed with water (25 mL each 3 times) to make them free from solvents. Agglomerate obtained was free flowing and of spherical in shape (Table 1).

**Table 1:** Preparation of Spherical Agglomerates

| Batch | Drug | Polymers | % of Polymers | Bridging Liquid | Solvent |
|---|---|---|---|---|---|
| T1 | Telmisartan | PVP | 1 | Dichloromethane | Dimethyl formamide |
| T2 | Telmisartan | PVP | 2 | Chloroform | Dimethyl formamide |
| T3 | Telmisartan | PVP | 3 | Ethyl Acetate | Dimethyl formamide |
| T4 | Telmisartan | PVP | 1 | Dichloromethane | Dimethyl Sulfoxide |
| T5 | Telmisartan | PVP | 2 | Chloroform | Dimethyl Sulfoxide |
| T6 | Telmisartan | PVP | 3 | Ethyl Acetate | Dimethyl Sulfoxide |

### Characterization of the Spherical Agglomerates

### Micrometric Properties of Spherical Agglomerates [7, 8]

By randomly counting the average diameter of 100 particles using an optical particle counter, the mean particle size of Telmisartan and its agglomerates was calculated. We calculated the bulk density, tap density, Carr's index, and angle of repose.

### Determination of Yield [9]

The weight of the dried finished product in relation to the starting total weight of the drug and polymer used to make the crystals was used to compute the practical yield of crystals, and the current practical yields were estimated using the formula below.

$$\textbf{Practical yield} = \frac{\text{practical mass of crystals}}{\text{Theoretical mass of drug and polymer}} \times 100$$

### Percentage Drug Content [10]

Spherical crystals containing 50 mg of Telmisartan were triturated and dissolved in a solvent system containing 10 mL of DCM in order to determine the drug content of the medication. Whatmaan filter paper 41 (pore size 0.45 m) was used to filter appropriately diluted samples before Telmisartan's medication content was measured spectrophotometrically at 291 nm. The formula shown below was used to compute the % drug content.

$$\textbf{Percentage Drug Content} = \frac{\text{practical drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

### *In-Vitro* Dissolution Studies Spherical Crystals [11]

Telmisartan spherical crystal dissolution tests were carried out in 900 mL of phosphate buffer pH 7.5 using a USP type II dissolution test apparatus (United States Pharmacopoeia, 2006).

For each dissolving investigation, a temperature of 37±0.5°C and 100 rpm stirring were provided. For each dissolving investigation, spherical crystals corresponding to 100 mg of telmisartan were employed. Periodically, samples were taken, and the dissolving media was changed. Telmisartan concentration was measured spectrophotometrically at 291 nm on a UV-visible spectrophotometer after filtration through Whatman filter paper 41 (pore size 0.45 m).

## RESULT AND DISCUSSION

### Micrometric Properties of Spherical Agglomerates

The agglomerate formed was spherical (Fig. 1) in nature. Micrometric properties of Telmisartan are improved after the Spherical Agglomerates. The excellent angle of repose, Bulk Density, Tapped Density, Carr's Index (%) and Haunser Ratio were observed (Table 2). Batch T6 Telmisartan Spherical Agglomerates were showing the optimum result.

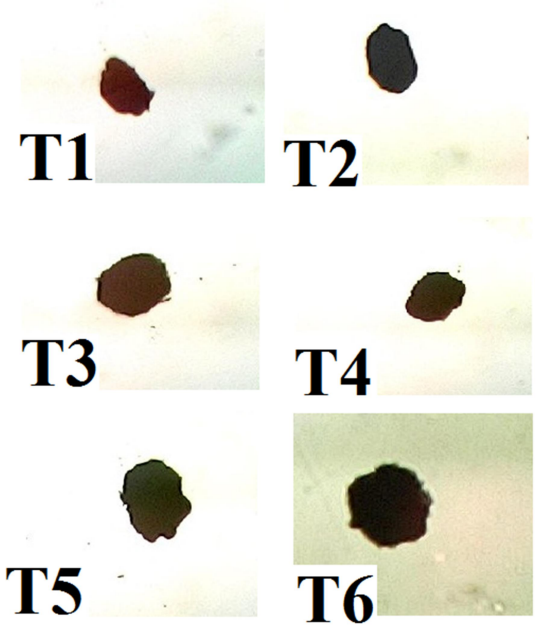


**Figure 1:** Optical Microscope View of Spherical Agglomerates

**Table 2:** Micrometric Properties of Spherical Agglomerates

| Formulation Code | *Angle of Repose(Θ) | * Bulk Density (gm/mL) | *Tapped Density (gm/mL) | *Carr's Index (%) | *Haunser Ratio |
|---|---|---|---|---|---|
| T1 | 33.79±0.26 | 0.3456±0.026 | 0.4498±0.031 | 23.16 | 1.52 |
| T2 | 31.92±0.35 | 0.3471±0.032 | 0.4352±0.035 | 20.24 | 1.44 |
| T3 | 29.38±0.32 | 0.3510±0.034 | 0.4324±0.029 | 18.82 | 1.36 |
| T4 | 28.74±0.39 | 0.3542±0.042 | 0.4290±0.022 | 17.43 | 1.27 |
| T5 | 26.32±0.24 | 0.3584±0.033 | 0.4245±0.027 | 15.57 | 1.21 |
| T6 | 19.56±0.29 | 0.3596±0.029 | 0.4227±0.024 | 10.60 | 1.11 |

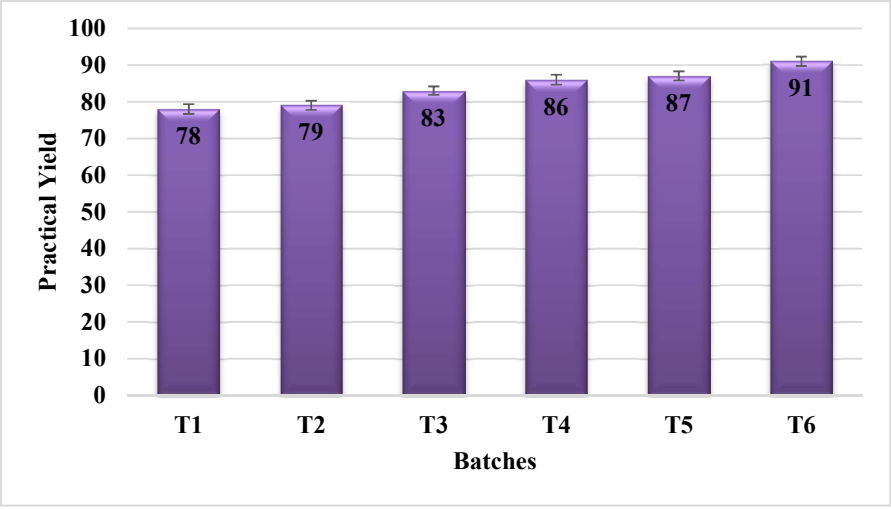


**Figure 2:** Percentage Practical Yield of Prepared Formulations

**Practical Yield**

Practical yield of prepared agglomerates was obtained in the range of 76 ± 1.30 to 91 ± 1.28 as shown in the Table 3 and Fig. 2. The production yield of crystals increases as concentration of PVP increases in DMSO solvent as compared with DMF. Ethyl acetate plays an excellent role of bridging liquid as compared with dichloromethane and chloroform.

**Drug Content:**

All the formulation showed good drug content and maximum drug was found to be 92.2 ± 1.22 % in batch T6 (Table 4 and Fig. 3).

***In-Vitro* dissolution Studies Spherical Crystals**

Spherical agglomerates showed higher dissolution rate. Agglomerates with PVP 3% have shown 93.26% drug release within 45 min in batch T6 (Table 5 and Fig. 4). As a result, PVP is thought to accelerate the dissolution of Telmisartan in agglomerates as concentration increases, possibly as a result of an increase in hydrophilicity. Additionally, the wettability of the crystallized product is improved by the bridging liquid, which is thought to speed up the pace of disintegration.

**Table 3:** Percentage Practical yield of Telmisartan Spherical Agglomerates

| Formulation Code | Percentage Practical yield of Telmisartan (%) |
|---|---|
| T1 | 78 ± 1.30 |
| T2 | 79 ± 1.24 |
| T3 | 83 ± 1.16 |
| T4 | 86 ± 1.32 |
| T5 | 87 ± 1.22 |
| T6 | 91 ± 1.28 |

(± Shows Each Value is mean of Three Determination)

**Table 4:** Drug Content of Telmisartan Spherical Agglomerates

| **Formulation Code** | **Drug Content (%)** |
|---|---|
| T1 | 83.2 ± 0.21 |
| T2 | 84.1 ± 0.27 |
| T3 | 87.5 ± 0.35 |
| T4 | 85.4 ± 0.24 |
| T5 | 90.4 ± 0.38 |
| T6 | 92.2 ± 0.22 |

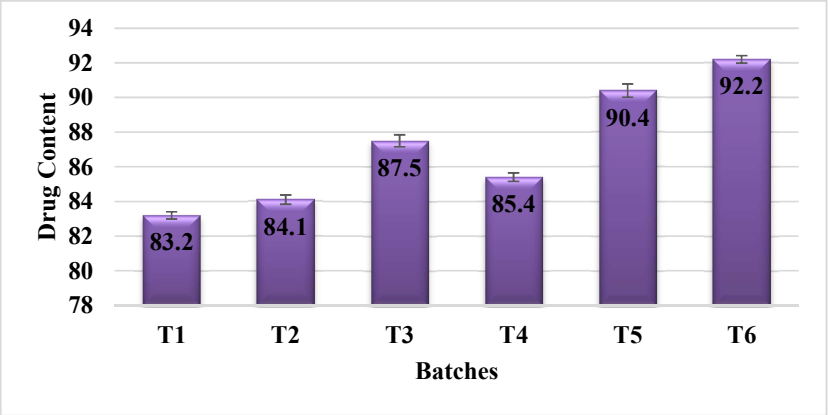


**Figure 3:** Drug Content of Telmisartan Spherical Agglomerates

**Table 5:** Percentage Drug Release of Telmisartan Spherical Agglomerates

| Batch / Time (min) | T1 | T2 | T3 | T4 | T5 | T6 |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 27.63 | 29.51 | 31.62 | 34.02 | 36.95 | 41.23 |
| 10 | 32.14 | 36.48 | 42.74 | 47.21 | 50.08 | 53.54 |
| 15 | 38.94 | 46.57 | 51.14 | 57.62 | 61.23 | 64.41 |
| 20 | 49.63 | 53.24 | 58.21 | 64.36 | 68.17 | 70.69 |
| 30 | 61.26 | 67.56 | 72.47 | 75.06 | 78.54 | 81.45 |
| 45 | 71.69 | 74.27 | 81.03 | 84.56 | 89.45 | 93.26 |

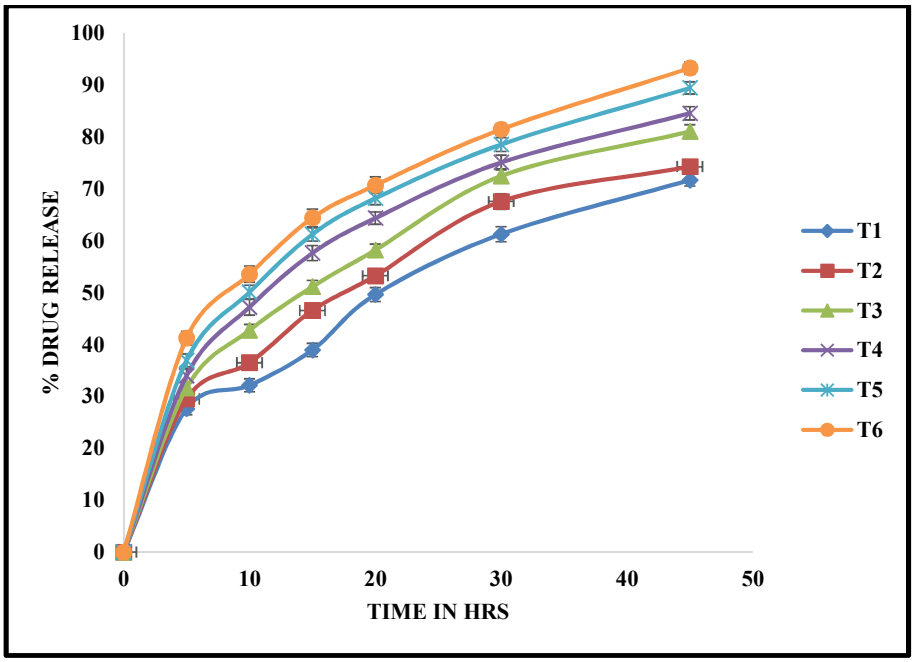


**Figure 4:** Percentage Drug Release of Telmisartan Spherical Agglomerates

## CONCLUSION

The spherical crystallization approach was effectively used in the current work to create spherical agglomerates of telmisartan. The generated spherical agglomerates' altered size and form suggested a changing crystal habit, which may be to blame for the greatly enhanced flowability, solubility, and dissolution characteristics of Telmisartan agglomerates. Agglomerates' micromeritics characteristics were greatly enhanced, enabling successful direct tableting. Batch T6 show the optimum result and as compared to other batches.

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