Macromolecular Research

Article

DOI 10.1007/s13233-021-9029-0

www.springer.com/13233 pISSN 1598-5032 eISSN 2092-7673

Release Behavior of Telmisartan/Amlodipine Combination Drug According to Polymer Type

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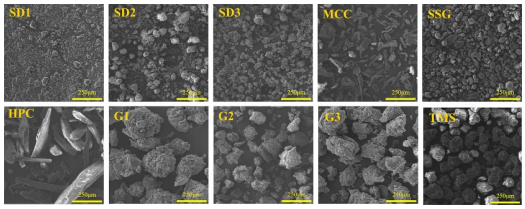
Received October 27, 2020 / Revised February 5, 2021 / Accepted February 13, 2021

Abstract: Patients at risk for hypertension with comorbidities such as diabetes and metabolic syndrome often require two or more antihypertensive drugs to lower their blood pressure. Telmisartan and amlodipine are widely known drugs to treat hypertension. However, telmisartan suffer of poor solubility in water that makes necessary to increase its dosage to reach a sufficient therapeutic concentration. In this study, a solid dispersion containing a water-soluble polymer was prepared to make the absorption rate of telmisartan similar to that of amlodipine, a water soluble drug. As water-soluble polymers, polyvinylpyrrolidone K30, polyethylene glycol 6000, and poloxamer 407 were used. The encapsulation of the solid dispersion was analyzed by differential scanning calorimetry, Xray diffraction, and high-performance liquid chromatography. The reduced flowability of the solid dispersion was improved by a wet granulation. Scanning Electron Microscopy was used to study the morphology and the flowability was verified by measuring the angle of repose, bulk density, and tap density, and expressed by Hausner ratio and Carr index. The release behavior was confirmed by dissolution test and high-performance liquid chromatography. As result we proved that telmisartan a higher release rate when encapsulated with PVP K30. Finally, we designed a drug formulation in which amlodipine and telmisartan could be absorbed at a similar rate.



Keywords: telmisartan, amlodipine besylate, solid dispersion, soluble polymer, combination drug.

1. Introduction

To lower the blood pressure four typology of drugs are mainly used: diuretics, sympathetic nerve blockers, renin-angiotensin-based drugs, and calcium channel blockers.[1-4] Among them, amlodipine act as a calcium channel blocker. When the intracellular calcium concentration increases, muscle contraction and vasoconstriction occur increasing the blood pressure. Amlodipine acts as a blocker on the calcium channel forming a bind with the alpha 1 subunits constituting the calcium channel, thereby modifying the quaternary structure of the protein. These prevent the vasoconstriction and the increasing in blood pressure.[5]

Telmisartan is an angiotensin II receptor blocker. Renin, secreted from the renal cortex, converts angiotensinogen produced in the liver to angiotensin I, and subsequently a converting enzyme converts it to angiotensin II. The angiotensin II constricts blood vessels and increases blood pressure by reabsorbing water. Telmisartan, blocking angiotensin II receptors, is then effective in reducing the blood pressure. These two active pharmaceutical ingredients (amlodipine and telmisartan) has been proved to be effective when they are combined, because they are synergic, acting on different mechanism that regulates the same phenomenon, the increasing of the blood pressure. In particular, amlodipine was found to be more effective when used with an angiotensin receptor blocker than when both drugs are used alone.[6,7]

These two compounds have different classification based on their solubility. In particular, telmisartan is classified as Class 2 and amlodipine as Class 1 of the Biopharmaceutics Classification System (BCS).[8-10] BCS is a scientific classification system that classifies drug components based on solubility and permeability in aqueous solutions. Components in Class 1 have high solubility and permeability, while components in Class 2 have low solubility and high permeability. Therefore, it is necessary to increase the solubility of telmisartan to have a similar dissolution in combination drug. In this study, solid dispersions of telmisartan with a set of water-soluble polymers were prepared to increase its dissolution and, consequently, its bioavailability.[11,12]

Water-soluble polymers, commonly employed in drug delivery system, were used. We choose three different polymers, polyvinylpyrrolidone (PVP) K30, polyethylene glycol (PEG) 6000, and poloxamer 407. The combination of amlodipine, telmisartan, and binders was referred to reported studies.[13-15] Mannitol and microcrystalline cellulose (MCC) were used as excipients, sodium starch glycolate (SSG) as a disintegrant, hydroxypropyl cellulose (HPC) and water as a binder, and magnesium stearate

Acknowledgments: This research was supported by Basic Science Research Program (2020R1A2C2103089) and the bilateral cooperation Program (2019K2A9A1A06098563) of the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning.

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(Mg. st) as a lubricant.[16-19]

A solid dispersion was prepared by rotary evaporation after dissolving telmisartan and water-soluble polymer in methanol. The encapsulation of solid dispersion was confirmed by analyzing the crystallinity by differential scanning calorimetry (DSC) and X-ray diffraction (XRD), and then high-performance liquid chromatography (HPLC) was performed to measure the specific encapsulation efficiency. A wet granulation process was performed to improve the flowability decreased during the solid dispersion preparation. Granules were observed by a scanning electron microscope (SEM) in order to evaluate their morphologies. The improved flowability was confirmed by measuring the angle of repose, bulk density (BD), and tap density (TD) and calculating the Hausner ratio and a Carr index.[21-23] The wet granules were tabletted and the dissolution rate was tested by HPLC. Among them, the batch with the highest release rate were mixed with amlodipine to form a combination drug. The release rate of the formed combination drug was compared with the active pharmaceutical ingredient (API) and a commercially available tablet.

2. Experimental

2.1. Materials

Amlodipine besylate, Telmisartan, Polyvinylpyrrolidone (PVP) K30, Polyethylene Glycol (PEG) 6000, Poloxamer 407, Microcrystalline Cellulose (MCC), Mannitol, Hydroxypropyl cellulose (HPC), Sodium Starch Glycolate (SSG), and Magnesium Stearate (Mg. st) were purchased from Sigma-Aldrich, St. Louis, MO, USA. Tertiary distilled water and HPLC grade reagents were used. Neostar tablets® (Sinil Pharm, Korea) were used as commercially available tablets for comparison. Figure 1 shows chemical structures of active pharmaceutical ingredients (API) and water-soluble polymers.

2.2. Preparation of solid dispersion

Solid dispersions with different water-soluble polymers were prepared to increase the solubility of telmisartan. The composition of the three prepared batches is reported in Table 1. The solid dispersions were prepared with a method described elsewhere. Briefly, 5 g of water-soluble polymer was solubilized in 500 mL of methanol and mixed until the solution resulted to be clean, then 1 g of telmisartan was added and mixed until its dissolution. The solvent was then removed by evaporated using a rotary evaporator (N-1000, EYELA, Japan) to obtain a solid dispersion. To further reduce the solvent residue, the product was frozen and lyophilized by a freeze-dryer (FD8508, IlShin, Korea). The resulting solid dispersion was cryo-milled by freezer mill (Freezer mill 6750, SPEX, USA) and sieved to obtain a fine powder with a granulometry lower than 100 μm.

2.3. Structural analysis

Fourier Transform Infrared Spectroscopy (FTIR) was performed to understand if any physical and chemical structure changes occurred in the process of preparing the solid dispersion. The molecular structures of telmisartan, polymers and solid dispersions were analyzed by ATR-FTIR (GX, Perkin Elmer, Waltham, Massachusetts, USA) in the 4000-400 cm^{-1} range.

2.4. Thermodynamic and crystallographic analysis

DSC and XRD analysis were performed to confirm the encapsulation of telmisartan and the water-soluble polymer as crystallinity. It was analyzed by DSC (DSC 4000, Perkin Elmer, Japan). The amount of the sample was 5 mg, the heating rate was 30 °C/min, and the temperature range was from -10 °C to 290 °C. Samples were sufficiently laminated on a 0.3 mm transparent glass substrate and analyzed by XRD (MAX 2500 X-ray diffractometer, Rigaku, Japan). The interval size was 0.02°, the speed was 4°/min, the range was from 5° to 60°, the current was 30 mA, and the voltage was 40 kV.

2.5. Encapsulation efficiency analysis

The encapsulation efficiency was measured by HPLC to confirm that telmisartan was encapsulated into the water-soluble polymer without denaturation and loss. 240 mg of SD1, SD2, and SD3, and 40 mg of telmisartan were dissolved in 20 mL of methanol, respectively. 1 mL of each solution was taken and filtered through a 45 μm syringe filter (Tokyo Roshi Kaishm, Ltd., Japan) for HPLC

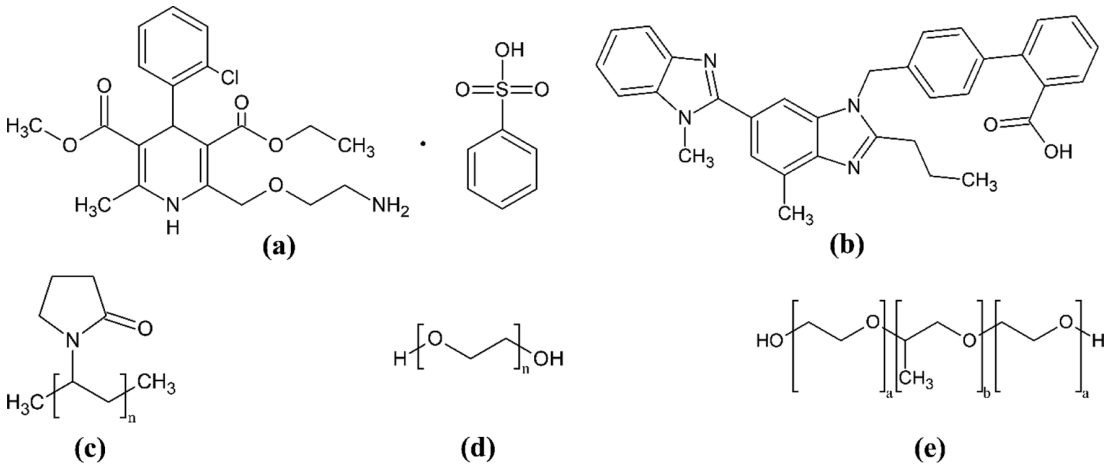

Figure 1. Chemical structures of (a) Amlodipine besylate, (b) Telmisartan, (c) PVP K30, (d) PEG 6000, and (e) Poloxamer 407.

Table 1. Formulation of the three batches (indicated by SD1, SD2, and SD3) of solid dispersion of Telmisartan within the water-soluble polymers[a]

Batch		SD1	SD2	SD3
API	Telmisartan		40	
Water-Soluble Polymers	PVP K30	200	0	0
	PEG 6000	0	200	0
	Poloxamer 407	0	0	200
Total			240	
Solid Dispersion Method		Rotary Evaporation (Solvent: Methanol)		

[a]Unit: mg.

analysis. An HPLC analyzer (NS-4000 HPLC System, Futecs, Korea) equipped with a 5 μm, 250×4.6 mm column (ProntoSIL C_{18} SH, Bischoff Chromatography, Germany), a column oven (AT-4000, Futecs, Korea), and an autosampler (NS-6000 Autosampler, Futecs, Korea) was used. The flow rate was 1.0 mL/min, the sample injection volume was 200 μL, the temperature was 30 °C, and the analysis time was 20 min. For the detection of telmisartan, the UV wavelength of 270 nm was used. According to the reported study, the mobile phase was mixed with methanol and acetonitrile in a volume ratio of 7:3.[24] The encapsulation efficiency of telmisartan in the solid dispersion was calculated by Eq. (1) in which m_{act} is the actual drug contents and m_{th} is the theorical drug contents.[25,26]

$$\text{Encapsulation efficiency (\%)} = \frac{m_{act}}{m_{th}} \times 100 \quad (1)$$

2.6. Wet granulation of solid dispersion

A wet granulation process was performed to improve the flowability reduced in the process of preparing the solid dispersion. (Table 2) HPC and distilled water was mixed at a concentration of 0.15 mg/μL to prepare the binding solution. The solution was then prepared accordingly to each batch to form the granules. To evaporate the moisture and the residual alcohol, they were dried in an oven. The product was then sieved with a 300 μm size to obtain uniform size granules.

2.7. Morphological analysis

The morphology of the particles was observed by scanning electron microscopy (SEM, S-3000N, Hitachi, Japan) with an acceleration voltage of 20 kV. A small amount of the particles was placed on the stub with carbon tape. The particles were then coated with palladium-platinum by sputtering (SC7640, Quorumtech, UK).

Table 2. Formulation of the granules (indicated as G1, G2, G3) starting from the respective batches of solid dispersion (SD1, SD2, and SD3)[a]

Batch		G1	G2	G3
Solid Dispersion	SD1	240	0	0
	SD2	0	240	0
	SD3	0	0	240
Diluent	MCC		40.5	
Disintegrating agent	SSG		15	
Binder	HPC		1.5	
	Water		20	
Total			297	
Granulation Process			Wet	

[a]Unit: mg.

2.8. Flowability analysis

To compare the flowability of telmisartan, solid dispersion, and granules, several parameters were calculated. The angle of repose was calculated by the Eq. (2) using the height (h) and radius (r) when the particles were stacked. Bulk density (BD) and tap density (TD) were measured according to the 12th revision of the Korean Pharmacopoeia. The Hausner ratio and the Carr index were calculated by Eq. (3) and Eq. (4) to evaluate flowability.[27,28]

$$\text{Angle of repose} = \text{Arctan}(h/r) \quad (2)$$

$$\text{Hausner ratio} = \frac{V_b}{V_t} \quad (3)$$

$$\text{Carr index (\%)} = \frac{V_b - V_t}{V_b} \times 100 \quad (4)$$

(V_b: bulk density, V_t: tap density)

2.9. Tablet manufacturing and dissolution behavior

1% Mg st was added in each granule and tableted to prepare 3 batches of tablet (T1, T2 and T3 from G1, G2, and G3, respectively). Among the three batches T1, which had the highest dissolution rate, was tableted within Amlodipine to make a combination drug following the composition described in Table 3. A dissolution tests and HPLC analysis was then performed to compare the dissolution rates of the combination drugs with a commercially available drug. The dissolution test was carried out by the first method (rotary specimen tube method) described in the 12th edition of the Korean Pharmacopoeia. The solution was prepared accordingly to the following recipe, 2 g of sodium chloride was dissolved in 7 mL of hydrochloric acid then DI water was added to reach 1000 mL, the pH of the obtained solution was 1.2. A dissolution tester (DST-610, Labfine, Korea) was used to compare the behavior of the prepared tables, the rotational speed was set at100 rpm, the temperature at 37 ± 0.5 °C, and the volume of solution to 900 mL. At each timepoints (0, 5, 10, 15, 30, 45, 60, 90, and 120 min) 1 mL of solution was with-

Table 3. Formulation for Telmisartan/Amlodipine combination drug[a]

Telmisartan	Granule	297
	Mg. st	3
Amlodipine	Amlodipine	5
	Mannitol	50
	MCC	39
	SSG	5
	Mg. st	1
Total		400

[a]Unit: mg.

draw to further analysis and refilled with 1 mL of fresh solution. The taken eluate was filtered through a 45 μm syringe filter and analyzed by HPLC. High-performance liquid chromatography (NS-4000 HPLC, Futecs, South Korea) was performed with an autosampler (NX-6000 autosampler, Futecs, South Korea) and a silica gel column (Intersil® OSD-3 C18, GL Science Inc, South Korea). The eluent was flux in the column at a rate of 1.0 mL/min, and the sample injection volume was set to 100 μL for analysis. The UV wavelength of the detector was set to 273 nm. The mobile phase was obtained by mixing acetic acid (CH_3COOH), buffer (pH 4.5), and acetonitrile (C_2H_3N) 0.015 mM, in a ratio of 88:12 (v/v%). The mobile phase was then stirred for 1 h and evenly mixed using an ultrasonic grinder.[29]

3. Results and discussion

3.1. Structural analysis

IR spectrum (Figure 2) of telmisartan exhibited characteristic broad peaks at 3261 cm^{-1} (N-H stretch), 2950 cm^{-1} (aliphatic C-H stretch). The first peak was observable also in all the SD samples. Other characteristic peaks of telmisartan were centered at 1584 cm^{-1} (aromatic C=C bend and stretch), at 750 cm^{-1} (C-H bending), at 1018 cm^{-1}, and at 1075 cm^{-1}. These last two indicates the presence of aromatic C-H in plane stretch. It should be noticed that the fingerprint in the area between 500 cm^{-1} and 1500 cm^{-1} of the telmisartan spectra clearly indicated the presence of aromatic groups. The presence of several of these peaks in the solid dispersions SD1, SD2, SD3, where the telmisartan was encapsulated, indicates that the denaturation did not occur in during the process.[30]

3.2. Thermodynamic and crystallographic analysis

Figure 3 shows the results of the DSC analysis. Telmisartan showed an endothermic peak at about 260 °C, PVP K30 had no apparent endothermic peak, and PEG 6000 and poloxamer 407 had an endothermic peak at about 60 °C. The peaks individu-

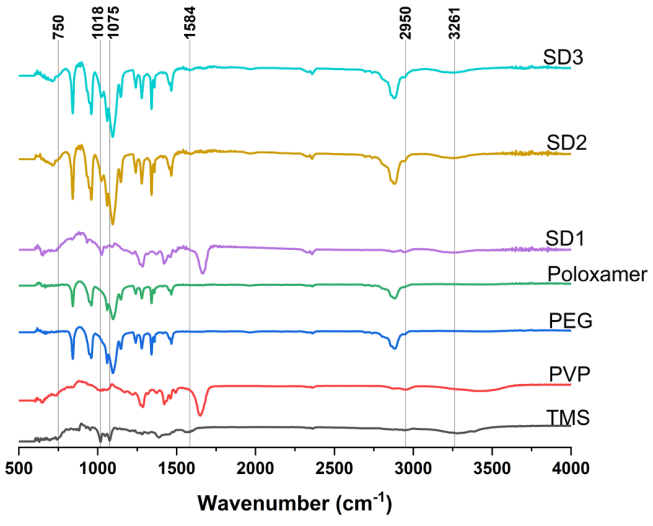

Figure 2. FTIR spectra of Telmisartan, PVP K30, PEG 6000, Poloxamer 407 and Solid Dispersion SD1, SD2, and SD3.

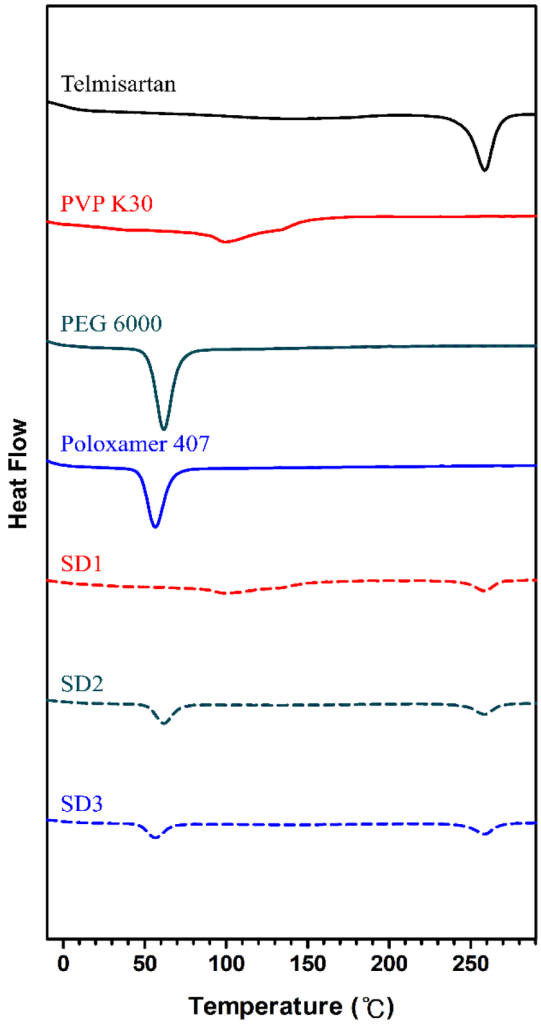

Figure 3. DSC thermograms of Telmisartan, PVP K30, PEG 6000, Poloxamer 407 and Solid Dispersion SD1, SD2, and SD3.

ated in the telmisartan and water-soluble polymers thermograms were observed in SD1, SD2 and SD3. The XRD analysis results are shown in Figure 4. Telmisartan had weak diffraction peaks from 5° to 50°. PEG 6000 and poloxamer 407 showed diffraction peaks at 19° and 23°, the similarity of their diffraction peaks is due to the fact that both polymers included PEG as functional group. PVP K30 had no visible diffraction peaks therefore its structure resulted to be amorphous in contrast with the crystalline structure of PEG 6000 and poloxamer 407. Peaks of telmisartan (with reduced intensity) and water-soluble polymers were observed in SD1, SD2, and SD3. The decreasing in the intensity of the peaks associated with the telmisartan of both DSC thermogram and XRD spectra in the solid dispersions when compared with the raw drug, indicates that telmisartan was successfully encapsulated in the water-soluble polymer. In addition, SD2 and SD3 showed reduced crystallinity, and SD1 had no crystallinity. The lack of crystalline structure was revealed to be advantageous in terms of dissolution.

3.3. Encapsulation efficiency analysis

The encapsulation efficiency was calculated by Eq. (1), using

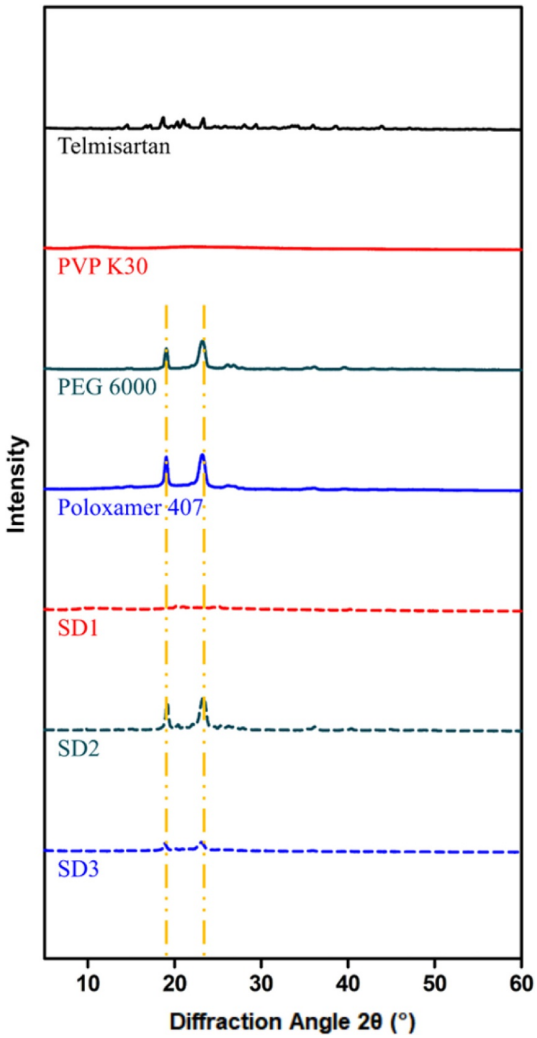

Figure 4. XRD patterns of Telmisartan, PVP K30, PEG 6000, poloxamer 407 and solid dispersion SD1, SD2, and SD3.

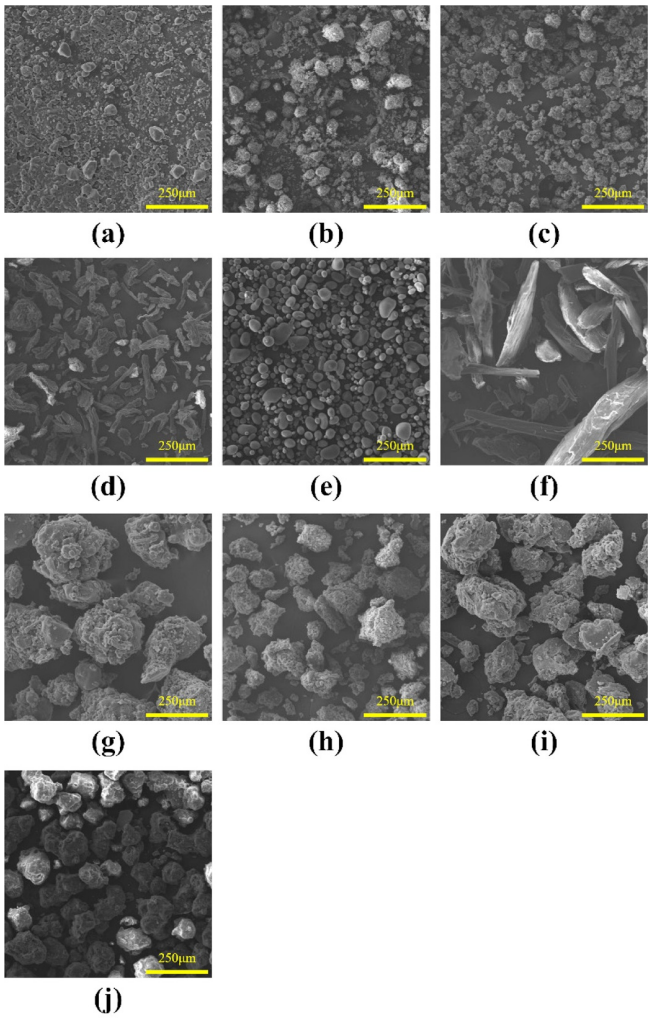

Figure 5. SEM images of (a-c) solid dispersions, (d) MCC, (e) SSG, (f) HPC, (g-i) granules, and (j) Telmisartan. The particle size of the solid dispersion resulted to be small, while their size increased by the use of excipients such as MCC, SSG, and HPC.

Table 4. Encapsulation efficiency of SD1, SD2, and SD3

	Encapsulation efficiency (%)
SD1	98.76 ± 0.20
SD2	99.13 ± 0.24
SD3	98.65 ± 0.26

actual drug contents and theorical drug contents. The encapsulation efficiency of SD1, SD2, and SD3 as reported in Table 4 converged to almost 100%. All the three considered polymers were almost perfectly efficient in encapsulating the telmisartan.

3.4. Morphological analysis

Figure 5 shows the results of SEM analysis. Because the solid dispersions were prepared by sieving with a size of 100 μm and freeze grinding only particles smaller than 100 μm were observed (Figure 5(a)-(c)). The morphology of MCC (Figure 5(d)), and HPC (Figure 5(f)) was crystalline with elongated crystals in the 70 μm-80 μm range in the first case 500 μm-600 μm in the latter. The morphology of SSG resulted instead to be spherical with a diameter between 20 μm-30 μm (Figure 5(e)). Since the granules were prepared starting from particles with dimeson lower than 100 μm, they were observed as lumps with diameters in the 200 μm-300 μm range. As expected, the granules were made of smaller particles condensed together (Figure 5(g)-(i)). This indicated the success of the wet granulation procedure. In addition, the absence of particles larger than 300 μm indicated the correct dissolution of the HPC during the procedure.

3.5. Flowability and tabletability

The results of the flowability analysis are shown in Table 5, and the flowability and tabletability were evaluated in Table 6. As general rule, smaller angles of repose gives smaller Hausner ratios, and, consequently, smaller Carr indexes and greater flowabilities.[31,32] Powders or granules with low flowability cause various difficulties in the pharmaceutical industry. In particular, flowability is an essential parameter in the tableting process among the many particle properties required for the production of solid dosage forms.[33] Each solid dispersion SD1, SD2, and SD3 had a Poor-grade flowability with an angle of repose of 47.25°, 43.45°,

Table 5. Flowability of solid dispersions and granules

	AOR	BD	TD	H	C	Flowability
SD1	47.25 ± 1.180	0.51 ± 0.006	0.70 ± 0.012	1.36 ± 0.013	26.66 ± 0.710	Poor
SD2	43.45 ± 0.450	0.42 ± 0.004	0.55 ± 0.005	1.31 ± 0.010	23.63 ± 0.570	Poor
SD3	40.61 ± 0.560	0.44 ± 0.004	0.56 ± 0.004	1.26 ± 0.007	20.57 ± 0.420	Poor
G1	31.38 ± 0.480	0.59 ± 0.005	0.66 ± 0.006	1.13 ± 0.008	11.21 ± 0.650	Good
G2	28.70 ± 0.420	0.472 ± 0.005	0.51 ± 0.007	1.09 ± 0.010	7.56 ± 0.850	Excellent
G3	27.25 ± 0.260	0.487 ± 0.007	0.51 ± 0.010	1.05 ± 0.008	4.51 ± 0.750	Excellent

Table 6. Flow character of Hausner ratio and Carr index

Flow character	Hausner ratio	Carr index
Excellent	1.00-1.11	≤10
Good	1.12-1.18	11-15
Fair	1.19-1.25	16-20
Pasable	1.26-1.34	21-25
Poor	1.35-1.45	26-31
Very poor	1.46-1.59	32-37
Very, very poor	> 1.60	> 38

40.61°, a Hausner ratio of 1.364, 1.310, 1.259, and a Carr index of 26.66%, 23.63%, and 20.57%, respectively. Instead, the granule produced from the solid dispersion (G1, G2, G3) had an excellent-grade of flowability with an angle of repose of 31.38°, 28.70°, 27.25°, a Hausner ratio of 1.126, 1.082, 1.047, and a Carr index of 11.21%, 7.56%, and 4.51%, respectively. Flowability analysis revealed that the wet granulation process had a positive effect on improving flowability and tableting properties. In addition, a lubricant is often added to the granular powder to increase flowability. In this study, tablets were prepared adding a Mg. st as lubricant.[34,35]

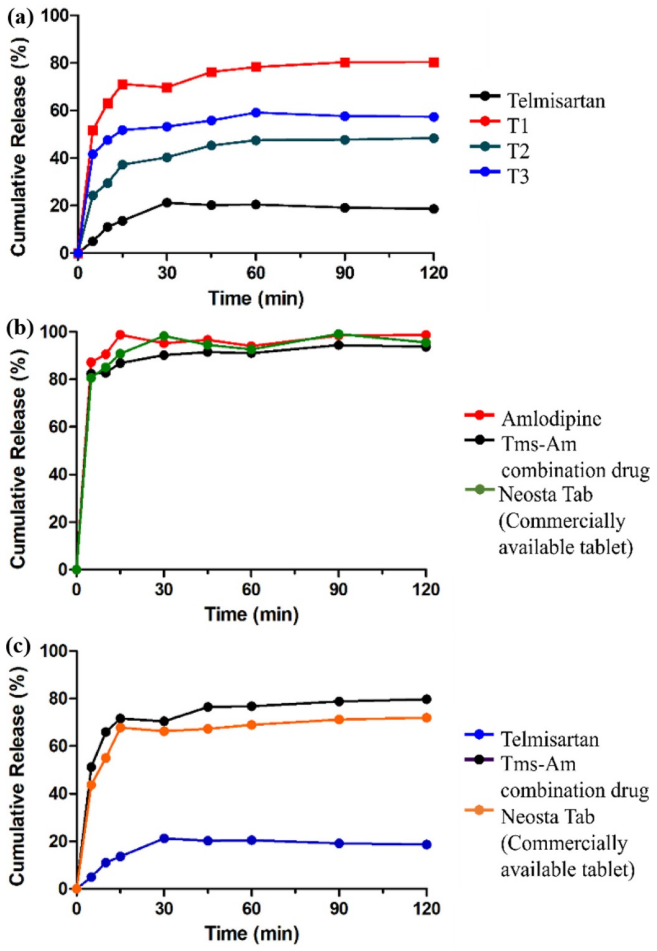

Figure 6. Dissolution behavior of (a) Telmisartan and Batch T1-3, (b) Amlodipine, Amlodipine of combination drug, and Neosta Tab®, (c) Telmisartan, Telmisartan of combination drug, and Neosta Tab®.

3.6. Dissolution behavior

The dissolution rate analysis for the prepared tablets is shown in Figure 6. Batches T1, T2, and T3 encapsulated with the water-soluble polymers all showed higher dissolution rates than the bare telmisartan, and among them, tablets encapsulated with PVP K30 showed the highest dissolution rate (Figure 6(a)). Since water-soluble amlodipine besylate is a highly soluble drug, there was no significant difference in the dissolution rate between our combination drug and the commercial product (Neostar Tablet®) as shown in Figure 6(b). However, telmisartan, which has a low solubility, showed a higher dissolution rate in the combination drug and Neostar Tablet® than in the API with a slightly better performance of our formulation (Figure 6(c)). The increased dissolution rate of telmisartan in the combination drug was similar to that of amlodipine besylate.

4. Conclusions

A combination drug of telmisartan and amlodipine was designed to increase the effect of hypertensive drugs. In this study, the API was encapsulated with a water-soluble polymer to form a solid dispersion to improve the solubility of telmisartan then a wet granulation was performed to improve the flowability prior to the tablet formation. Analysis of the properties of the solid dispersions and wet granules were performed. DSC and XRD analysis revealed that PVP K30 was amorphous and telmisartan, PEG 6000, and poloxamer 407 were crystalline. Furthermore, these analyses proved that telmisartan resulted, after the formation of the solid dispersions, well encapsulated inside the water-soluble polymers, in fact the crystallinity disappeared or decreased in the XRD spectra. The encapsulation efficiency was tested by HPLC, and for all the prepared batches it resulted to be close to 100%. The successful granulation was proved by SEM. The reduced flowability of the solid dispersions was improved during the granulation process and tested by the angle of repose, the bulk density and the tap density. As results of the dissolution test we could conclude that the solid dispersion

encapsulated with PVP K30 had the highest release rate. Starting from this composition, a combination drug was formed adding the amlodipine besylate. The dissolution of the amlodipine did not show a significant difference between the combination drug and the commercially available drug because of its high solubility. Telmisartan combined with PVP K30 in our composition, showed a higher release rate than the commercially available drugs. Through the dissolution test we were able also to confirm that the two drugs combined in our formulation can be absorbed at the same rate. We were able to prove that the dissolution rate of poorly soluble drugs can be improved by tableting the solid dispersion made of telmisartan and water-soluble polymer by wet granulation.

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