ABSTRACT: Telmisartan suffers from low oral bioavailability due to its poor water solubility. The research work presents a formulation of solid dispersed (SD) telmisartan formulation as a ternary mixture of a drug, a polymeric carrier (polyvinylpyrrolidone) (PVP K30), and an alkalizer (Na₂CO₃). The preparation method, which was lyophilization of an aqueous solution containing the ingredients, was free from any organic solvent. The developed SD formulations resulted in a significant improvement in in vitro dissolution (>90% drug dissolution in 15 min) compared to pure telmisartan. Solid-state characterization by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and X-ray diffraction (XRD) studies indicated the conversion of crystalline telmisartan into an amorphous form. Fourier transform infrared (FTIR) spectroscopy revealed the drug−polymer interaction that was responsible for reducing the chances of recrystallization. A short-term stability study showed that selected SD formulations were stable in terms of in vitro dissolution and retained their amorphous structure in ambient and accelerated conditions over 2 months. Selected formulations (drug/PVP K30/Na₂CO₃ as 1:1:2 or 1:2:2 weight ratio) resulted in >2.48 times relative oral bioavailability compared to marketed formulations. It was considered that the incorporation of an alkalizer and a hydrophilic polymer, and amorphization of telmisartan by lyophilization, could enhance in vitro dissolution and improve oral bioavailability.

INTRODUCTION

Low aqueous solubility of active pharmaceutical ingredients (APIs) causes poor dissolution in the gastrointestinal tract, which in turn may hinder its oral bioavailability.¹ Hence, the formulation scientists need to overcome the challenge of low aqueous solubility, especially for oral dosage form design. More specifically, drugs that undergo dissolution rate-limited absorption, mainly biopharmaceutical classification system (BCS) class-II drugs with poor solubility but high permeability, are common candidates for solubility or dissolution rate enhancement.² Different approaches to developing formulations or drug delivery systems for such a class of drugs have been adopted by pharmaceutical researchers and industries. The approaches include but not limited to micronization of APIs,³ nanoemulsions,⁴ self-emulsifying delivery systems,⁵ inclusion complexes,⁶ solid dispersion (SD),⁷ etc. Solid dispersion or dispersion of API in a fully or partially amorphous form or solid solution in a suitable carrier matrix is one of the effective and easy-to-adopt techniques to improve the apparent solubility of the API.

Solid dispersion can be prepared by many ways such as melt mixing, hot-melt extrusion, and solvent evaporation by a rotary evaporator or spray dryer or freeze dryer. It is not wise to conclude which method is the best because each has its pros and cons. For instance, melt extrusion is an industrially scalable method and free from solvent use but needs a low-melting-point polymeric carrier and requires that the API should be heat-stable at the melting temperature of the carrier.⁸ In the other hand, spray drying could use low temperatures but its inherited complexity in terms of process optimization and final product attributes are among the major challenges.⁹ Lyophilization or freeze-drying is another method of preparing solid dispersion.¹⁰ Principally, it works on prefreezing and sublimation under low pressures and hence devoid of applying heat. Therefore, it is suitable for formulating heat-sensitive APIs into solid dispersion. Lyophilization allows a fully
aqueous solution to be converted into powder, which has made it an environmentally friendly “green” approach. The method of preparation of solid dispersion has a significant impact on product properties such as the degree of amorphization and stability. Hence, the selection of a desirable method is very important for solid dispersion. In our research, we have adopted the lyophilization technique to prepare a telmisartan (TEL) solid dispersion system.

Telmisartan (TEL) (chemical name, 4′-(((1,4′-dimethyl-2′-propyl(2,6′-bi-1H-benzimidazol)-1′-yl)methyl)-(1,1′-biphenyl)-2-carboxylic acid) is an angiotensin receptor II blocker. They have dissolved the drug in methanol and employed the spray drying technique. Compared to their work, in our research, we have employed the freeze-drying technique using the only aqueous vehicle. The use of organic solvents has been avoided. The innovator’s telmisartan tablet formulation, Micardis (Boehringer Ingelheim) consists of sodium hydroxide as an alkalizer and meglumine and sorbitol as a solubilizing agent or water-soluble inactive excipients. The tablet also contains povidone and magnesium stearate. In the developed formulation by the present research, we have reduced the number of excipients using one alkalizer and one hydrophilic polymer only. The developed formulation was characterized for the solid-state property by diffusion thermal calorimetry (DSC), Fourier transform infrared (FTIR) spectroscopy, scanning electron microscopy (SEM), and powder X-ray diffractometry (PXRD). Two separate 2 months of stability studies in accelerated and ambient conditions were carried out. Finally, the developed formulation was subjected to an in vivo study in an animal model to assess the oral bioavailability and compare it with the marketed product.

### RESULTS AND DISCUSSION

**Solubility of Telmisartan.** Telmisartan, classified as a poorly water-soluble drug, resulted in 0.004 g/L solubility in water. However, it showed higher solubility in an acidic medium (pH 1.2) due to the presence of two imidazole groups. The resulting solubility values of telmisartan in our experiments were 0.524, 0.026, and 0.007 g/L in 0.1 N HCl, phosphate buffer pH 7.5, and phosphate buffer pH 6.8, respectively, which mean that the lowest solubility was in normal distilled water and the highest was in the acidic medium. Due to poor solubility but high permeability, telmisartan is categorized as a drug under BCS class II and exhibits pH-dependent solubility. The saturation solubility of telmisartan is quite higher in the acidic medium. Again, in a basic medium with increasing pH, telmisartan solubility increases. At pH 7.5, telmisartan solubility is higher than that at pH 6.8. The solubility of ionizable telmisartan increases with highly acidic or highly basic pH, but at neutral pH, it decreases. A similar fashion of pH-dependent telmisartan solubility was observed by other researchers.

**Miscibility with PVP K30.** Miscibility study results showed that with increasing polymer concentration from 1 to 7%, the solubility of telmisartan in the aqueous polymeric medium increases in a good linear fashion (Figure 1). In the previous study also, we have observed the same phenomena with PVP K30 and other polymers. The ΔG° values calculated from the miscibility study were all negative and within the range of...
The increasing amount of the hydrophilic polymer can increase drug solubility. Although the exact mechanism is not clear, it can be assumed that a weak drug–polymer complex is one of the reasons. The drug and polymer may interact by forming different types of interactions such as hydrogen bonds, electrostatic interactions like ion-ion or dipole–dipole interactions, etc.\(^2\) PVP K30 was chosen as a polymeric carrier because of its high compatibility with many drugs, high melting point, high tolerance in the human body, and high popularity as a carrier in solid dispersion to prevent crystalline drug precipitation while maintaining supersaturated state in the gastrointestinal medium.\(^3\) The linear relationship between the PVP K30 concentration and drug solubility has strengthened the selection of PVP K30 for the research. The Gibbs free energy is calculated to assess the spontaneity of the solubilization process. In this study, all \(\Delta G^\circ_t\) values are negative at all polymeric concentrations, indicating the spontaneous nature of solubilization. Generally, decreasing negative values of \(\Delta G^\circ_t\) (-<0) indicates better solubilization and the values are also proportionate to the concentration of polymeric carriers.\(^4\) In accordance with the theory, in our research, the highest concentration of PVP K30 (7%) has resulted in the lowest Gibbs energy value and the highest drug solubility, indicating a favourable reaction. The studies could go beyond 7% polymeric concentration, but to restrict the amounts of inactive ingredients or carrier, we have not studied PVP K30 concentrations beyond 7%.

**Lyophilization.** The major advantages of the lyophilization method include the ability to use no organic solvent and the formation of fine amorphous particles. In our reported method of preparing solid dispersion, we have not used any organic solvent. We have introduced one homogenization step by an overhead homogenizer in preparing colloidal dispersion of the ingredients before prefreezing. In our preliminary study (data not shown), we have observed that lyophilized dry powder, obtained from homogenized dispersion, resulted in higher drug solubility compared to that of nonhomogenized one. High-speed homogenization can reduce the size of solutes in the medium, which could be distributed evenly at fine particle size throughout the medium. Homogenization at a high pressure followed by lyophilization is often applied to prepare a nanoparticulate system such as solidified nanodispersion.\(^5\) Valsartan has been prepared a nanosuspension by homogenization followed by lyophilization, which showed enhanced drug release as a result of reduced particle size and increased surface area.\(^6\) In our research, we have used high-speed homogenization for better formation of colloidal dispersion before freeze-drying, which has eventually resulted in enhanced dissolution compared to nonhomogenization (data not shown). All of the solid dispersion formulations reported in this article have been prepared following the same methodology. The final powder was loose, white powder that could be easily recoverable from the glass apparatus. The yield of the final product recovered from the glass container was >92% in all cases.

**%Drug Content.** The results of the analysis of the drug content (%) considering the quantity of powders equivalent to 40 mg of telmisartan for solid dispersion formulations was found to be within the range of (99.15 ± 1.16)–(101.2 ± 1.23), and these values are within the acceptable range (Table 1). Low values of standard deviation (SD) for the drug content indicate uniformity in drug distribution in all of the solid dispersion formulations.

### Table 1. Drug Content of Telmisartan in Different Solid Dispersion Formulations

| formulations | % drug content   |
|--------------|------------------|
| F1           | 101.2 ± 1.23     |
| F2           | 100.5 ± 0.92     |
| F3           | 101.05 ± 0.79    |
| F4           | 99.2 ± 1.31      |
| F5           | 99.59 ± 1.91     |
| F6           | 101.24 ± 0.66    |
| F7           | 99.88 ± 1.55     |
| F8           | 99.15 ± 1.16     |
| F9           | 100.79 ± 0.48    |
| F10          | 99.95 ± 1.33     |
| F11          | 100.22 ± 0.55    |
| F12          | 99.59 ± 1.19     |
| F13          | 99.53 ± 1.12     |

**Selection of Optimum Formulation Based on In Vitro Dissolution Study.** The dissolution medium as per the compendia for telmisartan is phosphate buffer pH 7.5. The same medium was used to screen the developed SD\(_{telmi}\) formulations prepared as per Table 4 with varying concentrations of Na\(_2\)CO\(_3\) and PVP K30. Two formulations (F12, F13) were prepared without Na\(_2\)CO\(_3\) to compare the effect of alkalizer on in vitro dissolution. The result of the in vitro dissolution study is presented in Figure 2. It was observed that there were significant differences in the in vitro dissolution profile between F12, F13, and other SD\(_{telmi}\). While the lowest percent dissolution from SD\(_{telmi}\) was 73% in 60 min (F8), F12 and F13 showed percent drug dissolution of only 26.14 and 30.33% in 60 min. The results showed that without the alkalizer, only PVP K30 in low concentrations (2 and 3 g with respect to 1 g of telmisartan) was not able to enhance the telmisartan dissolution significantly. Being a hydrophilic carrier matrix, PVP K30 has the ability to enhance dissolution of the poorly water-soluble drug, but in the case of telmisartan, a drug with pH-dependent solubility, the presence of an alkalizer matters significantly. In another study, the same phenomena have been reported, where without the alkalizer, PVP K30 alone (drug/PVP K30, 1:3 weight ratio) could not enhance telmisartan dissolution significantly.\(^6\) This dissolution en-
hancement occurred due to the modulation of micro-
environmental pH by the alkalizer in the formulation. In
the presence of the hydrophilic carrier, when the SD_{telmi} becomes
wet by the dissolution medium, Na_{2}CO_{3} starts dissolving
immediately. The pH of the surrounding microenvironment
increases to a high basic level, which makes telmisartan soluble
at a higher rate and extent. This enhanced dissolution is
attributed to the enhanced solubility of telmisartan in
the presence of Na_{2}CO_{3}.

In vitro dissolution profiles with respect to time for all
formulations studied have been described in Figure 3. Out of
all 11 SD_{telmi} formulations, except F8, all of the 10 SD_{telmi}
formulations resulted in more than 90% dissolution within 15
min. However, the marketed product resulted in 76.57% drug
release within 15 min. Pure telmisartan powder resulted in very
low (less than 5%) drug dissolution within 60 min. Out of the
11 SD_{telmi} formulations (F1−F11), the lowest concentration of
Na_{2}CO_{3} was 2 g with respect to 1 g of drug. Statistical analysis
using one-way analysis of variance (ANOVA) (Tukey test)
showed no significant difference in the dissolution of F1−F11
except for F8 at 15 min with the p-value <0.05 (Figure S1).

Figure 3. In vitro dissolution profile of all SD_{telmi} formulations,
marketed formulation (marketed TEL), pure telmisartan (pure TEL),
physical mixture (PM F1 and PM F2). The value within parentheses
against each formulation represents the composition by weight ratio
of telmisartan/PVP K30/Na_{2}CO_{3}. Each time point is representative
of mean data ± SD (n = 3).

Although the drug−polymer miscibility study showed that
increasing polymer concentration shall increase drug solubility
in the aqueous medium, but from the dissolution profile
derived in this research, no such effect of polymer
concentration−solubility relationships in in vitro dissolution
could be established. By Figure 4, if we compare the
dissolution at 5 min between different formulations of fixed
Na_{2}CO_{3} but varying PVP K30, we can see that increasing PVP
K30 causes lesser dissolution. For instance, in Figure 4A, the
order of drug dissolution at 5 min is F1 > F2 > F3 > F6 > F9
with the highest at 91.56% (F1) and the lowest at 81.67%
(F9). The same trend was observed in the case of F4, F7, and
F10 (Figure 4B). PVP K30, due to its hydrophilic nature,
reduces interfacial tension to dissolution medium that
contributes to drug wettability. Increased drug wettability
causes the formation of a microenvironment surrounding the
particles and enhances solubilization. PVP K30 solubilizes the
drug and maintains a supersaturated state in the gastro-
intestinal fluid without precipitation. But after a certain level
of concentration, PVP K30 forms a gel-like layer surrounding
the particle. Water penetrates slowly through the layer and
drug dissolution occurs via erosion. After a certain time,
erosion becomes complete and drug dissolution occurs rapidly.
That is why at 15 min or later time points drug dissolution
becomes almost equal in all SDs (Figure 4C). Only F8 showed a
cumulative dissolution of 71.24% within 60 min, which is the
lowest among all SD_{telmi} formulations with the highest
concentration of the alkalizer.

To assess the effect of freeze-drying on the dissolution of
solid dispersion, we have compared in vitro dissolution of the
physical mixture of telmisartan, Na_{2}CO_{3}, and PVP K30 in two
compositions like F1 and F2, termed as PMF1 and PMF2,
respectively. The cumulative percent dissolution of telmisartan
from PMF1 and PMF2 was 69.18 and 73.34%, respectively, in
60 min (Figure 3). The result was comparable with the
marketed tablet but lower than all SD_{telmi}. These results
indicated that other than the presence of PVP K30 and
Na_{2}CO_{3}, the nature of the lyophilized powder also influences

Figure 4. In vitro dissolution profile of all solid dispersed telmisartan coded as (A) F1, F2, F3, F6, F9; (B) F4, F7, F10; and (C) F5, F8, F11. The
value within parentheses against each formulation represents the composition by weight ration of telmisartan/PVP K30/Na_{2}CO_{3}. Each time point
is representative of mean data ± SD (n = 3).
the drug dissolution. Here comes the benefit of solid dispersion. In solid dispersion, the drug either remains completely miscible with the carrier to form a homogeneous amorphous dispersion or it forms an amorphous suspension in the carrier.\textsuperscript{28} Such molecular-level dispersion or amorphization increases drug solubility that eventually enhances drug dissolution.

Hence, the enhancement of dissolution from lyophilized SDtelmi is attributed to three different factors: modulation of microenvironmental pH by Na\textsubscript{2}CO\textsubscript{3}, beneficial effects from PVP K30, and conversion of the crystalline drug to amorphous or molecular dispersion. Therefore, further solid-state characterization was carried out with selected SDtelmi to evaluate the physical state of lyophilized powder. From \textit{in vitro} dissolution study, three SDtelmi were chosen which are F1, F2, and F3 due to the three lowest concentrations of inactive ingredients with the highest benefits as the most suitable formulations.

**Functional Group Analysis.** Functional group analysis has been done by attenuated total reflection (ATR)-FTIR study to assess the interaction between telmisartan−PVP K30 and Na\textsubscript{2}CO\textsubscript{3}. If any structural change in telmisartan occurs within SDtelmi, then it may lead to change in functional groups. That is why change or loss in crystallinity can be assumed from infrared spectra. In pure telmisartan spectra (Figure 5), the characteristic peak was obtained at 1694.11 cm\textsuperscript{-1}, which is attributed to the C═O stretching of the carboxyl group. Other significant peaks observed in pure telmisartan spectra include 3059.60 cm\textsuperscript{-1} (aromatic C−H stretching), 2956.04 cm\textsuperscript{-1} (aliphatic C−H stretching), and 1603 cm\textsuperscript{-1} (aromatic C═C bending and stretching). All of the characteristic peaks are in close agreement with previously reported functional group analysis for telmisartan.\textsuperscript{15} PVP K30 is characterized by strong absorption bands at 1658.72, 2948.29, and 1283.84 cm\textsuperscript{-1} as a result of C═O stretching of the carbonyl group, C−H, and N−C stretching, respectively (Figure 5A).\textsuperscript{29} The adsorbed moisture in PVP K30 had caused an absorption band of 3250−3500 cm\textsuperscript{-1} with a peak at 3411.12 cm\textsuperscript{-1}. All of the peaks including the absorbed moisture peak were also evidenced in our previous study.\textsuperscript{7} The spectra of Na\textsubscript{2}CO\textsubscript{3} showed the characteristic band at 1423.15, 1065.99, and 878.08 cm\textsuperscript{-1}, indicating similarity with the reported Na\textsubscript{2}CO\textsubscript{3} spectrum.\textsuperscript{30} In both of the physical mixture (1:1 weight ratio) of telmisartan individually with PVP K30 and Na\textsubscript{2}CO\textsubscript{3}, major characteristic peaks of the drug are visible, indicating no significant interaction of telmisartan with other components in the dry mix state. In PM\textsubscript{telmi} which is an equimolar physical mixture of three components (Figure 5A), peaks of telmisartan at 3059.60, 2956.04, and 1603 cm\textsuperscript{-1} remain unchanged. However, the peak at 1694.11 cm\textsuperscript{-1} was present with reduced intensity. There might be two reasons: either peaks responsible for the amide group of PVP K30 suppresses the telmisartan peak in the surrounding region of 1600 cm\textsuperscript{-1} infrared wave number or H bonding has been taken place involving the −COOH group. However, in the telmisartan−PVP K30 mixture spectra, the peak at 1694.11 cm\textsuperscript{-1} was visible, which is adjoining with C═O stretching spectra of PVP K30 at 1658 cm\textsuperscript{-1}. So, it nullifies the first reason. Therefore, it can be assumed that some degree of interaction occurred during the physical mixing of telmisartan with the other two components. In the spectra of SD\textsubscript{telmi} of F1, F2, and F3, telmisartan peaks at 1694.11, 3059.60, and 1603 cm\textsuperscript{-1} are completely absent, which are indicative of interaction involving −COOH group (Figure.
A decrease in the peak intensity due to the lowering of vibration or the absence of carbonyl stretching from the $-\text{COOH}$ group along with an absence of the $\text{O}–\text{H}$ band at 3100 cm$^{-1}$ indicates the formation of strong H bonding between two components. $^{14}$ PVP K30 can form H bonding either through nitrogen or carbonyl group of pyrrole ring present in its structure. $^{31}$ Absence of the C==O peak at 1694.11 cm$^{-1}$ indicates the formation of H bonding between $-\text{COOH}$ of telmisartan and the carbonyl functional group of PVP K30 in SD$_\text{telmi}$. The dominant peak visible at around 1600 cm$^{-1}$ was the peak of C==O stretching of PVP K30 at 1658.72 cm$^{-1}$. There was no difference of characteristic peaks of telmisartan in terms of the position or intensity between F1, F2, and F3, which means that the different ratio of PVP K30 did not cause any difference in interaction with telmisartan, visible by infrared spectra.

Drugs in an amorphous state in a solid dispersion have a tendency to precipitate rapidly into the dissolution medium because of the supersaturated solution state. A polymeric carrier like PVP K30 inhibits such precipitation by prolonging supersaturation. $^{12}$ The exact mechanism of how the polymer acts as a precipitation inhibitor is still not fully clear, but it is established that polymers like PVP K30 cause some interaction with the drug. Drug precipitation or recrystallization occurs by nucleation followed by crystal growth. A suitable polymeric carrier in solid dispersion interrupts either nucleation or crystal growth by interaction with the drug. Hydrogen bonding is the most possible way of drug–polymer interaction that not only increases the activation energy for nucleation but also inhibits crystal growth. Hence, in this research, possible H bonding between PVP K30 and telmisartan, evidenced by FTIR study, can be responsible for enhanced dissolution as well as inhibition of recrystallization of solid dispersed telmisartan. Further structural change of telmisartan in SD$_\text{telmi}$ was evaluated by SEM followed by thermal analysis and finally PXRD study.

**Surface Morphology Study.** The morphologies of all three components, PM$_\text{telmi}$ and three different SD$_\text{telmi}$ (F1, F2, and F3) were evaluated by SEM analysis, and the micrographs were obtained as the results (Figure 6). Pure telmisartan is observed as a long needle-shaped homogeneous crystal with a smooth texture in the SEM image, which is similar to previous studies. $^{26}$ Na$_2$CO$_3$ and PVP K30 were observed as irregular fragments and round-shaped particles, respectively, in the individual micrograph. In the ternary physical mixture of telmisartan, Na$_2$CO$_3$, and PVP K30, needle-shaped telmisartan crystals and irregular fragments of Na$_2$CO$_3$ are distributed on the surface of round-shaped PVP K30. It can be said that telmisartan still retains its crystalline structure in the ternary mixture. The micrograph of SD$_\text{telmi}$ (F1, F2, and F3) showed the absence of any definite structural shape of the telmisartan crystal. There was no difference observed apparently between SEM images of three formulations. The absence of the telmisartan crystal image indicates the structural change of the drug crystal that might be attributed to the conversion of the crystalline drug to the amorphous state by lyophilization. However, the SEM micrograph is not very conclusive in this case. Therefore, the change in crystallinity is further assessed by thermal analysis and PXRD study.

**Thermal Analysis.** Thermal analysis gives an idea of the physical nature of solid dispersed powder and melting and crystallization behavior. In this research, the DSC study was done to analyze the samples with the application of controlled heat. The results are recorded as DSC thermograms (Figure 7). Pure TEL presented a sharp endothermic peak at about 271.74 °C, which corresponded to its intrinsic melting point, indicating that all TEL crystals melted at that temperature and there was no moisture adsorbed due to its highly hydrophobic nature. $^{34}$ PVP K30 had shown a broad endothermic band from 90 to 150 °C with a curve at 142 °C, which corresponds to the melting range of PVP K30. During thermal scanning of PVP K30, evaporation of residual moisture was observed by a broad band due to the extremely hygroscopic nature of the PVP polymer. $^{7}$ Physical mixture (PM) had shown one small endothermic band at around 140 °C and a small endothermic peak at 269.99 °C, corresponding to PVP K30 and telmisartan, respectively. The endothermic peak in the physical mixture for TEL shifted a little bit from 271.74 to 269.99 °C. This little peak shifting occurs due to melting point depression, which may occur for an individual component if mixed with another component. The endothermic peak of TEL in the physical mixture was sharp but with reduced intensity. Such reduction of intensity might happen from partial amorphization of telmisartan in the physical mixture during sample preparation, which was also evidenced by PXRD but contradicted with the SEM image. Another reason might be partial solubilization of telmisartan in melted PVP K30 during DSC analysis. $^{29}$
was no new peak generated in the physical mixture, indicating no physical incompatibility between the components of a ternary mixture containing the drug, PVP K30, and Na2CO3. There was no intrinsic characteristic peak for Na2CO3 over the entire range of temperature tested from 25 to 300 °C in the physical mixture due to its high melting point of 851 °C, as reported in other studies.19 In the thermogram of SDtelmi (F1, physical mixture due to its high melting point of 851 °C, F2, and F3), no sharp endothermic peak of telmisartan was visible. It is inferred that there was no presence of telmisartan crystals in the sample. We have assumed the formation of an amorphous particle in the lyophilized solid dispersion. However, the DSC study alone is not capable of determining the physical state of the developed product alone. Therefore, the lyophilized dispersions were further evaluated by PXRD analysis.

**Crystallinity Analysis.** PXRD tests were done to evaluate the structural change of telmisartan in the physical mixture and lyophilized formulations (F1, F2, and F3). Telmisartan, as observed in the SEM image, remains as a distinct homogeneous shaped crystal. In XRD diffractograms (Figure 8), distinctive peaks with noticeable intensities were visible for telmisartan at 2θ angles of 6.8, 14.2, 19.1, and 22.3° with intensities (cps) of 1095(33), 702(26), 166(13), and 252(16), respectively. Such peaks have been observed for telmisartan by other researchers also,20 which indicated its sharp crystal nature. PVP K30, being an amorphous polymer did not show any distinct peak (Figure 8). In the diffractogram of Na2CO3 (Figure 8), many peaks are visible but all above the 2θ angle of 23.76°, which means that these peaks would not interfere with telmisartan peaks. In an equimolar ternary physical mixture containing telmisartan, PVP K30, and Na2CO3, characteristic peaks of telmisartan were observed but with lower intensities. For instance, the peak at a 2θ angle of 6.8° had come up with an intensity (cps) of 92 (10), which is considerably lower than that of pure telmisartan. Again, the peak at 19.1° was absent in the physical mixture diffractogram. The absence of a distinct characteristic peak or reduction in the peak intensity in the diffractogram indicates complete or partial loss of crystallinity.18 During the preparation of the physical mixture sample for PXRD, a mild degree of cogrinding was performed using a mortar and pestle. Possibly during cogrinding, some loss of crystallinity occurred to telmisartan in the physical mixture. Cogrinding of the drug and inactive ingredients such as the polymer can cause partial amorphization of the crystalline drug. Zhong et al. has reported reduced peak intensity at a 2θ angle of 6.8° for telmisartan indicating conversion of the crystalline structure to amorphous by cogrinding with chitosan.16 However, such reduction in crystallinity in the physical mixture in our sample is not well correlated with SEM images, where the physical mixture showed a clear presence of telmisartan crystals. It can be said that SEM images are not capable of detecting partial loss of crystallinity, which is observed in the diffractogram.

All SDtelmi formulations (F1, F2, and F3) showed the same pattern in PXRD analysis. Characteristic telmisartan peaks at the above-mentioned 2θ angles were absent in all three lyophilized formulations. Peaks of Na2CO3 were present in the PXRD diffractogram. The absence of distinct characteristic peaks indicates the presence of a large amount of drug in the solution in solid state, and a reduction of a large number of characteristic peaks indicates amorphization of drug crystals.14 Therefore, it can be said that by lyophilization, telmisartan has been converted to an amorphous form in the presence of PVP K30 and Na2CO3, as a solid dispersion. This result is in close agreement with SEM images and FTIR analysis. In the SEM image, SDtelmi did not show any trace of telmisartan crystalline structure. In the FTIR spectrum, alteration in the functional structure. In the FTIR spectrum, alteration in the functional group indicated possible structural change. Moreover, in *in vitro* dissolution studies, higher dissolution rates have been achieved from SDtelmi behind which amorphization of telmisartan by lyophilization is one of the significant contributing factors. The poor water-soluble crystalline drug, when present in the amorphous form, usually has better aqueous solubility, which results in higher dissolution. This is because no energy is required to break the lattice structure, unlike the crystal form. It is speculated that in solid dispersion after dissolution if drugs precipitate, they remain in a metastable state, which has higher solubility.28 It is possible

---

**Figure 7.** DSC thermograms of pure telmisartan, PVP K30, ternary physical mixture of telmisartan/PVP K30/Na2CO3 (PM), and solid dispersion of telmisartan (F1, F2, F3).
An amorphous system is thermodynamically unstable and tends to convert into a more stable crystalline form, which is termed as recrystallization. The amorphous nature of the drug is one of the main contributing factors behind the improved dissolution of telmisartan from SD_{telmi}. Such improvement can be compromised by recrystallization of the drug in the solid dispersed system, which are induced by humidity and temperature. Such lyophilized solid dispersed powder particles had a wide surface area that is susceptible to adsorb moisture. Therefore, considering its importance, an assessment of the stability of SD_{telmi} was carried out in both ambient temperature/humidity as well as under elevated temperature/humidity (accelerated conditions). It is observed from the dissolution profile (Figure 9) that the plots of time vs cumulative percent drug dissolved at three different time points, in both types of studies, are almost super-imposable on one another for every single formulation. These results indicate that no change in the in vitro dissolution of telmisartan happened during two months of storage. It was assumed that there was no or negligible occurrence of recrystallization in the solid dispersed system. To confirm this assumption, PXRD study was done at 2 months of time point. It was observed from the PXRD diffractogram (Figure 10) that none of the characteristic peaks, mentioned in Section 3.8, had come out in any of the SD_{telmi} at 2 months of time point, indicating no recrystallization of the drug. Such a result is following the almost constant dissolution profile until the last sampling point.

The stability of solid dispersed amorphous powder depends on the type and concentration of the polymeric carrier. Two related factors are responsible for the stability of amorphous powder: molecular mobility and glass transition temperature ($T_g$). Molecular mobility is essential for molecular diffusion and surface integration. Diffusion causes amorphous phase separation inside the system. A drug rich with the amorphous phase is formed, which can relax toward molecular conformation and induces nucleation. Thereby, crystal growth starts and recrystallization occurs. Polymers, such as PVP, plays an important role in decreasing molecular mobility by increasing the $T_g$ of the solid dispersed system. At low $T_g$ values, an amorphous system can have sufficient molecular mobility to induce nucleation and crystal growth. Incorporating polymer with high $T_g$ insufficient amount can thereby make amorphous dispersion stable. In our study, PVP K30, used as the polymeric carrier, has played the role of a stabilizer for amorphous solid dispersions of telmisartan. Another factor of reducing crystal growth is strong drug–polymer interactions to form H bonding. To assess the H bonding between telmisartan and PVP K30, FTIR analysis was done at the last time point. From the infrared spectra (Figure S2), it was observed that the formation of H bonding was consistently evidenced by the absence of the characteristic telmisartan peak at 1695 cm\(^{-1}\) throughout the course of stability study for all three formulations at both conditions. Such strong H bonding between the drug and polymer is another responsible factor behind the stability of lyophilized solid dispersed telmisartan developed in this research. Adsorbed moisture on the solid dispersed system may act as a plasticizer for the polymer and can also break H bonding, weakening drug–polymer interaction. This may promote recrystallization. In our research, despite the presence of two moisture-sensitive components, hydrophilic polymer and Na\(_2\)CO\(_3\), moisture adsorption was not so much to cause crystallization, as to convert the poorly soluble crystalline drug to amorphous solid dispersion using a suitable polymer and method of preparation. In this research, amorphization of telmisartan was observed for F1, F2, and F3, despite the different amounts of the carrier, i.e., PVP K30 by the lyophilization method. Lyophilization is a well-established technique for amorphization of crystalline drugs, and therefore, it has been adopted to prepare solid dispersions. In this research, we have managed to cater to the advantages of lyophilization through the enhanced dissolution of telmisartan amorphous solid dispersion.

Stability Evaluation. A short-term stability study for 2 months was carried out under ambient and accelerated conditions with three SD_{telmi} formulations (F1, F2, and F3). In vitro dissolution profiles of three SD_{telmi} formulations (F1, F2, and F3) at 0 days and 1 and 2 months of time point are presented in Figure 9. Functional group analysis by FTIR and crystallinity study by PXRD has been done at 2 months of time point.

Figure 8. Powder X-ray diffractograms of (A) telmisartan, (B) PVP K30, (C) Na\(_2\)CO\(_3\), (D) ternary physical mixture of equal weight ratio of telmisartan/PVP K30/Na\(_2\)CO\(_3\), and (E–G) solid dispersion formulations of telmisartan (F1, F2, and F3).
evidenced in FTIR and PXRD studies. Suitable packaging is thus required to make amorphous dispersion stable for a long time.

**Pharmacokinetic Study.** The in vitro dissolution studies were followed by solid-state characterization and short-term (2 months) stability study of the developed SD_telmis. The results of all of these in vitro characterizations indicate the formation of lyophilized amorphous solid dispersion of telmisartan with enhanced in vitro dissolution. These results influenced us to proceed with in vivo pharmacokinetic studies to evaluate whether the in vitro beneficial effects of SD_telmis persist in in vivo conditions. From the three selected SD_telmis formulations (F1, F2, and F3), we have chosen F1 and F2 for pharmacokinetic study in the rat animal model because of lesser inactive ingredients compared to F3 with the same solid-state characters and benefits. A validated high-performance liquid chromatography (HPLC)−UV method within a linear range of 0.07−10 μg/mL and with 92.34−99.87% accuracy was employed to quantify telmisartan in rat plasma. The plasma concentration vs time profile for F1, F2, raw telmisartan powder, and marketed formulation is presented in Figure 11. Mean pharmacokinetic parameters, derived by noncompartmental analysis, with standard deviation, are presented in Table 2.

In terms of $C_{\text{max}}$, the order of different formulations is F2 > F1 > marketed telmisartan > raw telmisartan. $C_{\text{max}}$ determines the extent of drug absorption to the system. It was quite expected that raw telmisartan would generate the lowest $C_{\text{max}}$ because of its poor solubility. Although $C_{\text{max}}$ of F1 is higher than marketed telmisartan formulation, both values were the same statistically. The $C_{\text{max}}$ value of F2 is more than 2 times compared to that of F1, indicating a statistically significant
difference. This result is not in good correlation with in vitro dissolution results, where both of the formulations have shown >90% drug dissolution within 5 min. We assumed that the lower concentration of PVP K30 in F1 might be the reason. An amorphous dispersion, after administration, “springs out” the drug in the gastric medium causing a supersaturated zone around.32 In the gastrointestinal tract, PVP K30 prevents the drug to precipitate out as crystals from the supersaturated solution, which is termed as the “parachute” effect. The low amount of PVP K30 in F1, compared to that in F2, was not sufficient enough to inhibit the precipitation of telmisartan in the gastrointestinal tract, although in the in vitro medium, it did not cause any difference. The concentration of Na2CO3 was the same in F1 and F2. Therefore, it may be affirmed that the amount of PVP K30 in the F2 formulation made a difference in the plasma concentration of telmisartan compared to that in F1. However, such variation from in vitro to in vivo studies is a common occurrence. An in-depth study and replication of the study with a large number of animals could effectively evaluate the case. The values of t\text{max} in ascending order is F2 < raw telmisartan < marketed formulation < F1 (Table 2). Statistically, there was no difference in t\text{max} between raw telmisartan, marketed formulation, and F1. The t\text{max} of F2 was the lowest (0.5 h) among all four formulations, but it was statistically the same with the marketed formulation. t\text{max} determines the time taken to reach the C\text{max} and it stands for the rate of absorption. For BCS II class of drugs, if absorption is dissolution-rate-limited, then it enters the circulation immediately once a drug becomes soluble. Telmisartan, a BCS class II drug candidate, has excellent permeability.39 That is why, even from raw telmisartan, t\text{max} was quite faster regardless of the maximum concentration reached. However, the fastest absorption with the lowest t\text{max} was derived from lyophilized SD\text{telmisartan} (F2).

AUC\text{0-\infty} and AUC\text{0-\text{t}} were calculated to assess the total drug exposure to the system from various formulations and their relative bioavailability. As shown in Table 2, AUC\text{0-\infty} values of F1 and F2 were 2.54 times and 3.45 times higher than the marketed formulation, respectively. The AUC\text{0-\infty} value was the highest for F2, followed by those for F1, marketed formulation, and raw telmisartan. Relative bioavailability, calculated using AUC\text{0-\infty} values, is represented in Table 3. It showed that F2 and F1 resulted in 2.8 and 2.5 times higher relative bioavailability for the marketed formulation. Compared to raw telmisartan, their bioavailability was much higher (Table 3).

The improved relative bioavailability is a result of enhanced solubility and dissolution of telmisartan from lyophilized solid dispersion in the presence of the polymer and alkalizer. Improvement of aqueous solubility and dissolution, in turn, results in higher bioavailability because of the rapid and higher extent of absorption.40 Not only higher bioavailability but also point to point comparison from the plasma concentration vs time profile (Figure 11) also showed higher telmisartan absorption from F1 and F2 compared to the raw drug or marketed formulation.

### CONCLUSIONS

A solid dispersed formulation of telmisartan was prepared using PVP K30 as a polymeric carrier and Na2CO3 as an alkalizer by a lyophilization method. The preparation method came up with its advantage of not using any organic solvent or no application of heat. Telmisartan was converted to an amorphous form from its original crystalline structure, which helps in the improvement of solubility in the in vitro medium as well as in vivo. The pharmacokinetic study revealed that the lyophilized telmisartan formulation composed of a ternary system of the drug/polymer/alkalizer (1:2:2 weight ratio) had the highest relative bioavailability in rat with respect to the marketed formulation. It can be concluded that improved...
the medium in a capped glass bottle and shaken by an incubator shaker (Innova 4000) for 36 h at 100 rpm and 37 ± 2 °C. The aliquots were then centrifuged at 3000 rpm for 10 min. The supernatant layer was collected and filtered through 0.45 μm poly(tetrafluoroethylene) (PTFE) syringe filter (Thermo scientific, Germany) followed by measurement of absorbance by a UV spectrophotometer (Shimadzu 1800, Tokyo, Japan) at a wavelength of 231 nm after the required dilution. The concentration of the samples was determined using a suitably constructed linearity plot. Each study was done in triplicate.

**Miscibility Study.** Miscibility study of telmisartan with PVP K30 was done following the method reported by Kyaw et al. (2017). In short, an excess amount of telmisartan was added in 10 mL of different concentrations of PVP K30 solutions ranging from 1 to 7% (w/w) in a capped glass bottle. Then, the bottles were shaken by an incubator shaker following the same conditions as the solubility study. Aliquots were taken and the same process of sample preparation and measurements were followed as per the solubility study. The Gibbs free energy equation was applied to indicate the process transfer of telmisartan to the polymeric solution.22 Values of Gibbs free energy were calculated as per the following equation

\[ \Delta G^\circ = -2.303 RT \log(S_0/S_f) \]

where \( R \), \( T \), and \( S_0/S_f \) are the universal gas constant, the temperature in kelvin, and the ratio of molar solubility of telmisartan in an aqueous polymeric solution to that of pure water without the polymer, respectively.

**Preparation of Solid Dispersion.** Solid dispersion of telmisartan, henceforth termed as SD, was prepared by a lab-scale lyophilization or freeze-drying method incorporating PVP K30 and Na₂CO₃ in an aqueous medium. First, the aqueous solution of Na₂CO₃ was prepared according to the desired concentration. Then, the required amount of PVP K30 was dissolved in the Na₂CO₃ solution by constant stirring. After that, 1 g of telmisartan was added to the solution with constant stirring for 25 min, which is followed by homogenization for 5 min (4000 rpm) using an overhead homogenizer (WT130 Success Technic Industries, Malaysia). The colloidal dispersion was then kept for prefreezing at −80 °C for 24 h. After that, it was lyophilized or freeze-dried in a lab-scale freeze dryer (Alpha 1-2 LD plus Christ, Germany). The white powder, derived from a freeze dryer, was then hand-pulverized by a mortar and pestle, passed through a 350–500 μm sieve, and stored in a sealed air-tight plastic pouch in a vacuum desiccator until further evaluations.

**Determination of Drug Content.** Appropriate weight of telmisartan solid dispersion equivalent to 40 mg of telmisartan was dissolved in 50 mL of methanol and diluted appropriately to obtain a final concentration of 40 μg/mL. The samples were analyzed by the HPLC method. The drug content of the solid dispersions was determined in triplicate.

---

### Table 2. Pharmacokinetic Parameters of Telmisartan Derived after Oral Administration of Different Formulations of Telmisartan

| parameters          | raw telmisartan | marketed formulation | F1 (1-1-2) | F2 (1-2-2) |
|---------------------|-----------------|----------------------|-----------|-----------|
| \( C_{\text{max}} \) (μg/mL) | 0.164 ± 0.016   | 0.409 ± 0.175        | 0.611 ± 0.303 | 1.363 ± 0.229 |
| \( t_{\text{max}} \) (h)      | 1 ± 0.000       | 1.167 ± 0.764        | 1.667 ± 0.577 | 0.5 ± 0.00  |
| \( \text{AUC}_{0-\text{fl}} \) (μg h/mL) | 0.306 ± 0.080  | 1.206 ± 0.256        | 3.071 ± 1.189 | 4.161 ± 0.727 |
| \( \text{AUC}_{0-\text{inf}} \) (μg h/mL) | 0.333 ± 0.078  | 1.981 ± 0.493        | 4.876 ± 0.556 | 5.564 ± 0.630 |
| \( K_{\text{a}} \) (h⁻¹)       | 0.448 ± 0.074   | 0.252 ± 0.194        | 0.198 ± 0.110 | 0.241 ± 0.031 |
| \( T_{1/2} \) / (h)           | 1.575 ± 0.256   | 4.124 ± 2.917        | 4.802 ± 3.619 | 2.910 ± 0.390 |

*Each data is represented as mean data ± SD (n = 3). F1 and F2: solid dispersion formulations of telmisartan. The value within parentheses against each formulation represents the composition by weight ratio of telmisartan/PVP K30/Na₂CO₃.

---

### Table 3. Relative Bioavailability of Solid Dispersion Formulation of Telmisartan (F1 and F2) for Raw Telmisartan and Marketed Formulation

| formulations | % relative bioavailability (w.r.t. raw telmisartan) | % relative bioavailability (w.r.t. marketed formulation) |
|--------------|-----------------------------------------------|--------------------------------------------------------|
| raw telmisartan | 100 | 16.81 |
| marketed formulation | 594.87 | 100 |
| SD F1 (1-1-2) | 1464.31 | 246.15 |
| SD F2 (1-2-2) | 1670.86 | 280.88 |

---

**MATERIALS AND METHODS**

**Materials.** Telmisartan (TEL) (assay on the anhydrous basis, 99.8%) was purchased from Hangzhou Hyper Chemicals Limited, China, in the form of a white crystalline powder. PVP K30 was generously donated by IKOP Sdn Bhd, Malaysia. Na₂CO₃, potassium dihydrogen phosphate (KH₂PO₄), potassium hydroxide (KOH), and hydrochloric acid (37%) were procured from Merck KGaA, Germany. Acetonitrile for chromatography (HPLC grade), ethanol for plasma extraction (absolute for analysis), and methanol for dissolving telmisartan to prepare the standard solution (absolute for analysis) were also purchased from Merck KGaA, Germany. Purified water for HPLC was obtained from a Millipore system (18.2 MQ/cm resistivity, Milli-Q) (Millipore Corporation). Marketed telmisartan formulation, Teleact 40 mg tablet (Sun Pharma, Malaysia), was purchased from a local pharmacy.

**Solubility Study.** The solubility of raw telmisartan was determined in distilled water, 0.1 N HCl (pH 1.2), phosphate buffer solution pH 6.8, and phosphate buffer solution pH 7.5. An excess amount of telmisartan was added to 5 mL of each of the medium in a capped glass bottle and shaken by an incubator shaker (Innova 4000) for 36 h at 100 rpm and 37 ± 2 °C. The aliquots were then centrifuged at 3000 rpm for 10 min. The supernatant layer was collected and filtered through 0.45 μm poly(tetrafluoroethylene) (PTFE) syringe filter (Thermo scientific, Germany) followed by measurement of absorbance by a UV spectrophotometer (Shimadzu 1800, Tokyo, Japan) at a wavelength of 231 nm after the required dilution. The concentration of the samples was determined using a suitably constructed linearity plot. Each study was done in triplicate.

**Formulation of Telmisartan (F1 and F2) for Raw Telmisartan and Marketed Formulation**

Table 3. Relative Bioavailability of Solid Dispersion Formulation of Telmisartan (F1 and F2) for Raw Telmisartan and Marketed Formulation.

| formulations | % relative bioavailability (w.r.t. raw telmisartan) | % relative bioavailability (w.r.t. marketed formulation) |
|--------------|-----------------------------------------------|--------------------------------------------------------|
| raw telmisartan | 100 | 16.81 |
| marketed formulation | 594.87 | 100 |
| SD F1 (1-1-2) | 1464.31 | 246.15 |
| SD F2 (1-2-2) | 1670.86 | 280.88 |

---

Table 3. Relative Bioavailability of Solid Dispersion Formulation of Telmisartan (F1 and F2) for Raw Telmisartan and Marketed Formulation.

| formulations | % relative bioavailability (w.r.t. raw telmisartan) | % relative bioavailability (w.r.t. marketed formulation) |
|--------------|-----------------------------------------------|--------------------------------------------------------|
| raw telmisartan | 100 | 16.81 |
| marketed formulation | 594.87 | 100 |
| SD F1 (1-1-2) | 1464.31 | 246.15 |
| SD F2 (1-2-2) | 1670.86 | 280.88 |
In Vitro Dissolution Study. In vitro dissolution studies were carried out by a USP type II (paddle type) dissolution tester (Copley DIS 8000, U.K.). Phosphate buffer of pH 7.5 in a volume of 900 mL/basket was chosen as a dissolution study medium following the USP procedure. Other relevant parameters were as follows: speed of the stirrer, 75 rpm; temperature of the medium, 37 ± 0.5 °C; aliquot volume, 5 mL. At a predetermined time intervals of 5, 15, 30, and 60 min, sample aliquots (5 mL) from the dissolution basket were withdrawn and an equivalent amount (5 mL) of the fresh dissolution medium was immediately added to maintain a constant dissolution volume. The aliquots were filtered through a 0.45 μm syringe filter and analyzed by a predefined high-performance liquid chromatography (HPLC) method. Raw telmisartan powder (40 mg), marketed formulation 40 mg, ternary physical mixture of telmisartan–PVP K30–Na₂CO₃ (equivalent to 40 mg, composition as per F1 and F2), termed as PM1 and PM2, and all SDₜₐₜₐₘᵢ (equivalent to 40 mg) were used for in vitro dissolution studies.

In the HPLC method, used for dissolution sample analysis, the separation was achieved on a ZORBAX Eclipse Plus C₁₈ column (250 mm length and 4.6 mm internal diameter with 5 μm pore size). The isocratic elution method consists of 70:30 (v/v%) mixture of acetonitrile and 10 mM phosphate buffer solution (pH 3.8) as mobile phase, 1 mL/min flow rate, 10 μL injection volume, and UV detection system at 231 nm. Telmisartan was detected at approximately 4.8 min within a total chromatographic run time of 7 min.

Functional Group Analysis. Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) study was done to analyze functional groups present in telmisartan and SDₜₐₜₐₘᵰ to evaluate interactions between the drug and carriers. In this study, each of the components including telmisartan, physical mixture of all three components of the formulation in 1:1:1 weight ratio (henceforth termed as PMₜₐₜₐₘᵰ), and SDₜₐₜₐₘᵰ formulations were subjected to scanning over an IR range of 4000–4000 cm⁻¹ with accumulations of 15 scans at a resolution of 2 cm⁻¹ by an IR spectrometer (PerkinElmer, Waltham, MA). IR spectra were compared visually and analyzed to derive the outcome.

Surface Morphology Study. Scanning electron microscopy (SEM) was carried out to assess the surface and shapes morphology of SDₜₐₜₐₘᵰ particles. Pure telmisartan, pure PVP K30, pure Na₂CO₃, PMₜₐₜₐₘᵰ and SDₜₐₜₐₘᵰ were analyzed by SEM, and the generated micrographs were compared visually. In short, the method was as follows: using a pair of thumb forceps, double-sided carbon adhesive tape was placed on the flat surface of the SEM sample stub followed by a sprinkling of a very small amount of sample powder on it. Then, the sample particles were gold-coated and scanned for images using a scanning electron microscope (ZEISS EVO S0, Germany).

Thermal Analysis. Thermal analysis was done by differential scanning calorimetry (DSC) study. For this study, the sample (5–8 mg) was enclosed in an aluminum crucible and exposed to a thermal range of 10–300 °C (for PVP K30, up to 200 °C) (10 °C/min increment) in a differential scanning calorimeter (1-STARe, Mettler Toledo, Columbus, OH) under a constant nitrogen flow (10–20 mL/min). Pure telmisartan, PVP K30, PMₜₐₜₐₘᵰ and SDₜₐₜₐₘᵰ were used as samples. Na₂CO₃ alone was not studied by DSC due to its high melting point (around 850 °C), which is beyond the capacity of the instrument used.

Crystallinity Analysis. Assessment of crystallinity was done by powder X-ray diffraction (PXRD) analysis. The method followed was the method narrated by Tran et al. with minor modifications. Each of the individual components of the formulations including telmisartan, PMₜₐₜₐₘᵰ and SDₜₐₜₐₘᵰ was scanned using an X-ray diffractometer (Rigaku Ultima IV, TX) in increments of 0.02° from 3 to 80° at a rate of 1 s/step, where Cu Kα radiation used was 30 kV and 15 mA. Diffraction angles (2θ) were recorded along with intensity (counts), and an individual diffractionogram for each sample was derived.

Short-Term Stability Study. Two short-term stability studies (2 months of duration) were done with the final SDₜₐₜₐₘᵰ formulations in ambient (30 °C/75% relative humidity) and accelerated (40 °C/75% relative humidity) conditions using a stability chamber (M 1400, Capromax Sdn. Bhd., Malaysia) to evaluate significant changes during storage of the SDs if any. Samples were analyzed at 1 and 2 months by in vitro dissolution and compared to that of the 0 day result. PXRD and FTIR studies were also done at 2 months of time point.

Pharmacokinetic Study. A pharmacokinetic study was done in an animal model (rat) to evaluate the in vivo performances of developed SDₜₐₜₐₘᵰ formulations as well to determine their relative bioavailability compared to the raw drug and marketed formulation. The animal study protocol was prior approved by the Institutional Animal Care and Use Committee (IACUC-IIUM), International Islamic University Malaysia (reference no.: IJUM/S04/14/2/IACUC-Approval/2017(17)). This animal study had been carried out following the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications no. 8023, revised 1978).

Animal Husbandry and Maintenance. Male Sprague–Dawley rats weighing 280 ± 20 g and aged 9–10 weeks were purchased from Sapphire Enterprise, Selangor, Malaysia. The rats were housed as three rats per cage and acclimatized with the laboratory environment for one week on a standard 12 h light/dark cycle at a room temperature of 25 ± 3 °C and relative humidity of 50 ± 10%. The rats were provided with sufficient food and water during the acclimatization period. However, they were kept in the fasting condition with free access to water overnight (12 h) before the start of the experiment.

Study Design and Sample Collection. A total of 12 rats were divided into four groups (n = 3). Each of the groups received either pure telmisartan powder, marketed formulation or F1 and F2 (two different SDₜₐₜₐₘᵰ preparations selected after in vitro studies) by oral administration at a dose of 4 mg/kg body weight. For SDₜₐₜₐₘᵰ formulations, the equivalent amount

| Formulations | TEL (g) | PVP K30 (g) | Na₂CO₃ (g) |
|--------------|--------|------------|------------|
| F1           | 1      | 1          | 2          |
| F2           | 1      | 2          | 2          |
| F3           | 1      | 3          | 2          |
| F4           | 1      | 3          | 3          |
| F5           | 1      | 3          | 4          |
| F6           | 1      | 5          | 2          |
| F7           | 1      | 5          | 3          |
| F8           | 1      | 5          | 4          |
| F9           | 1      | 7          | 2          |
| F10          | 1      | 7          | 3          |
| F11          | 1      | 7          | 4          |
| F12          | 1      | 1          |            |
| F13          | 1      | 2          |            |
to the required dose was calculated and used for oral administration. The animal dose was calculated following the method described by Sengupta et al.,\textsuperscript{43} considering 40 mg as a human adult dose. The total study duration was 12 h.

At predetermined time intervals of 0.5, 1, 2, 4, 6, 8, and 12 h after dosing, 0.3–0.4 mL of blood sample was collected into ethylenediaminetetraacetic acid (EDTA) containing tubes from each rat through a retro-orbital artery. The rats were anesthetized every time by intraperitoneal pentobarbital injection. The samples were immediately centrifuged at 3000 rpm for 10 min. Separated plasma was collected and stored under \(-20 °C\).

**Plasma Extraction and Sample Analysis.** Before extraction, frozen plasma samples were thawed to ambient temperature. Pioglitazone (10 μL) as an internal standard (IS), equivalent to 5 μg/mL in plasma, was pipetted to 90 μL of each plasma sample in a centrifuge tube and vortexed for 1 min. The sample was then extracted with 1.5 mL of ethanol by vortex mixing for 5 min. The mixture was then centrifuged at 3000 rpm for 10 min to separate the organic layer. This organic layer was subjected to drying under a gentle stream of nitrogen. The dried residue was reconstituted with 200 μL of mobile phase and injected onto the HPLC system after filtering through a 0.22 μm PTFE syringe filter.

Quantitation of telmisartan was done by the HPLC method. The method was developed for biological sample analysis with slight modification in the mobile phase composition and run time of the analytical HPLC method, as described earlier (Selection of Optimum Formulation Based on In Vitro Dissolution Study) in this article. The HPLC parameters of the employed method were the following: reversed-phase; elution mode, isocratic; column, ZORBAX Eclipse Plus C18 (250 mm length, 4.6 mm internal diameter, 5 μm pore size); column temperature, ambient; mobile phase, 50:50 (v/v%) mixture of acetonitrile and 10 mM phosphate buffer solution (pH 3.8); flow rate, 1 mL/min; injection volume, 10 μL; chromatographic run time, 14 min; and detection, UV at 231 nm wavelength. The HPLC method was validated before analysis with a linear response within a range of 0.07–10 μg/mL. The accuracy and intraday and interday precision of the method were established following the standard acceptance criteria of bioanalytical method validation.\textsuperscript{44} The developed linearity plot was used to quantitate telmisartan in the plasma sample.

**Pharmacokinetic Parameters and Relative Bioavailability.** Plasma concentrations of telmisartan vs time point data were analyzed by noncompartmental analysis. The maximum plasma concentration (\(C_{\text{max}}\)) and time to reach \(C_{\text{max}}\) (\(t_{\text{max}}\)) were derived from the constructed plasma concentrations vs time plot. The area under curve (AUC\(_{0-\infty}\)) was calculated for every animal using the trapezoidal rule. AUC\(_{0-\infty}\) was calculated from AUC\(_{0-t}\) last detectable concentration, and elimination rate constant (\(k_{\ell}\)). \(k_{\ell}\) was calculated from the slope of the elimination phase. Finally, relative bioavailability was calculated comparing AUC\(_{0-\infty}\) of one formulation with another following eq 2.

\[
\text{rel. bio. of formulation 1} = \frac{\text{AUC}_{0-\infty}\text{of formulation 1}}{\text{AUC}_{0-\infty}\text{of formulation 2}}
\]

where rel. bio. of formulation 1 is the relative bioavailability of “formulation 1” with respect to that of “formulation 2.”

All pharmacokinetic data were subjected to ANOVA analysis (\(t\)-test) to evaluate the statistical significance of the difference between “means” of each group considering a 5% level of significance (\(p < 0.05\)).

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c04588.

Statistical analysis of in vitro dissolution of solid dispersion (SD) formulation of telmisartan at 15 min by one-way ANOVA (Figure S1) and FTIR spectra of three solid dispersed formulations A (F1), B (F2), and C (F3) at three-time points of the accelerated stability study (Figure S2) (PDF)

**AUTHOR INFORMATION**

**Corresponding Author**

Bappadiya Chatterjee — Department of Pharmaceutical Technology, Kulliyyah of Pharmacy, International Islamic University Malaysia (IIUM), Kuantan 25200, Malaysia; SPP School of Pharmacy & Technology Management, SVKM’s NMIMS, Mumbai 400056, India; orcid.org/0000-0003-1816-6028; Phone: +91 22 42332000; Email: bdpharmaju@gmail.com

**Authors**

Khater A. S. Al-Japairai — Department of Pharmaceutical Engineering, Faculty of Chemical and Process Engineering Technology, University Malaysia Pahang, Gambang 26300, Malaysia; Department of Pharmaceutical Technology, Kulliyyah of Pharmacy, International Islamic University Malaysia (IIUM), Kuantan 25200, Malaysia

Hala M. Alkhalidi — Department of Clinical Pharmacy, Faculty of Pharmacy, King Abdulaziz University, Jeddah 21441, Saudi Arabia

Syed Mahmood — Department of Pharmaceutical Engineering, Faculty of Chemical and Process Engineering Technology, University Malaysia Pahang, Gambang 26300, Malaysia

Samah H. Almurisi — Department of Pharmaceutical Technology, Kulliyyah of Pharmacy, International Islamic University Malaysia (IIUM), Kuantan 25200, Malaysia

Abd Almonem Doolaanea — Department of Pharmaceutical Technology, Kulliyyah of Pharmacy, International Islamic University Malaysia (IIUM), Kuantan 25200, Malaysia

Taha A. Al-Sindi — Department of Basic Medical Science, Kulliyyah of Medicine, International Islamic University Malaysia (IIUM), Kuantan 25200, Malaysia

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acsomega.0c04588

**Author Contributions**

The manuscript was written through the contribution of all authors. All authors have given approval to the final version of the manuscript.

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

The research was partially supported by the research grant provided by the Ministry of Higher Education, Malaysia (FRGS-17-006-572).
REFERENCES

(1) Gora, S.; Mustafa, G.; Sahni, J. K.; Ali, J.; Baboota, S. Nanosizing of valsartan by high pressure homogenization to produce dissolution enhanced nanosuspension: pharmacokinetics and pharmacodynamic study. Drug Delivery 2016, 23, 930–940.

(2) Khan, A.; Iqbal, Z.; Shah, Y.; Ahmad, L.; Ismail; Ullah, Z.; Ullah, A. Enhancement of dissolution rate of class II drugs (hydro-chlorothiazide); a comparative study of the two novel approaches; solid dispersion and liquisolid techniques. Saudi Pharm. J. 2015, 23, 650–657.

(3) Chatterjee, B.; Pal, T. Development and in vitro evaluation of micronized sustained release matrix tablet of carvedilol. Int. J. Pharm. Sci. Res. 2010, 1, 1–10.

(4) Choudhury, H.; Gorain, B.; Chatterjee, B.; Mandal, U.; Sengupta, P.; Tekade, R. K. Pharmacokinetic and pharmacodynamic features of nanoemulsion following oral, intravenous, topical and nasal route. Curr. Pharm. Des. 2017, 23, 2504–2531.

(5) Chatterjee, B.; Hamed Almuriisi, S.; Ahmed Mahdi Dukhan, A.; Mandal, U. K.; Sengupta, P. Controversies with self-emulsifying drug delivery system from pharmacokinetic point of view. Drug Delivery 2016, 23, 3639–3652.

(6) Wei, Y.; Zhang, J.; Zhou, Y.; Bei, W.; Li, Y.; Yuan, Q.; Liang, H. Characterization of galabridin/ hydroxypropyl-β-cyclodextrin inclusion complex with robust solubility and enhanced bioactivity. Carbohydr. Polym. 2017, 159, 152–160.

(7) Oo, M. K.; Mandal, U. K.; Chatterjee, B. Polymeric behavior evaluation of PVP K30-poloxamer binary carrier for solid dispersed nisoldipine by experimental design. Pharm. Dev. Technol. 2017, 22, 2–12.

(8) Thiry, J.; Lebrun, P.; Vinassa, C.; Adam, M.; Netchacovitch, L.; Ziemons, E.; Hubert, P.; Krier, F.; Esvard, B. Continuous production of itraconazole-based solid dispersions by hot melt extrusion: preformulation, optimization and design space determination. Int. J. Pharm. 2014, 453, 114–124.

(9) Singh, A.; Van den Mooter, G. Spray drying formulation of amorphous solid dispersions. Adv. Drug Delivery Rev. 2016, 100, 27–50.

(10) Sawicki, E.; Schellens, J.; Beijnen, J.; Nuijen, B. Pharmaceutical development of an amorphous solid dispersion formulation of elacridar hydrochloride for proof-of-concept clinical studies. Drug Dev. Ind. Pharm. 2017, 43, 584–594.

(11) Sengupta, P.; Das, A.; Ibrahim, F.; Mandal, U. K.; Chatterjee, B.; Mahnoood, S.; Das, S. K.; Kifayatullah, M. Safety profiling of pioglitazone and telmisartan combination by sub-chronic toxicity study in rat. Regul. Toxicol. Pharmacol. 2016, 81, 155–161.

(12) Cao, Y.; Shi, L.-L.; Cao, Q.-R.; Yang, M.; Cui, J.-H. In vivo characterization and oral bioavailability of organic solvent-free solid dispersions containing telmisartan. Iran. J. Pharm. Res. 2016, 15, 385.

(13) Bobbès, É.; Nagy, Z. K.; Nagy, B.; Balogh, A.; Forkas, B.; Tsiman, O.; Tsimen, K.; Sinkó, B. The effect of formulation additives on in vitro dissolution-absorption profile and in vivo bioavailability of telmisartan from brand and generic formulations. Eur. J. Pharm. Sci. 2018, 114, 310–317.

(14) Tran, P. H. L.; Tran, H. T. T.; Lee, B.-J. Modulation of microenvironmental pH and crystallinity of ionizable telmisartan using alkaliizers in solid dispersions for controlled release. J. Controlled Release 2008, 129, 59–65.

(15) Chandra, A.; Ghate, M. V.; Athal, K.; Lewis, S. A. In silico prediction coupled with in vitro experiments and absorption modeling to study the inclusion complex of telmisartan with modified beta-cyclodextrin. J. Inclusion Phenom. Macrocyclic Chem. 2018, 91, 47–60.

(16) Zhong, L.; Zhu, X.; Luo, X.; Su, W. Dissolution properties and physical characterization of telmisartan–chitosan solid dispersions prepared by mechanochemical activation. AAPS PharmSciTech 2013, 14, 541–550.

(17) Thapa, C.; Ahad, A.; Aqil, M.; Imam, S. S.; Sultana, Y. Formulation and optimization of nanostructured lipid carriers to enhance oral bioavailability of telmisartan using Box–Behnken design. J. Drug Delivery Sci. Technol. 2018, 44, 431–439.
(37) Janssens, S.; Van den Mooter, G. Physical chemistry of solid dispersions. *J. Pharm. Pharmacol.* 2009, 61, 1571−1586.

(38) Li, W.; Buckton, G. Using DVS-NIR to assess the water sorption behaviour and stability of a griseofulvin/PVP K30 solid dispersion. *Int. J. Pharm.* 2015, 495, 999−1004.

(39) Wienen, W.; Entzeroth, M.; van Meel, J. C.; Stangier, J.; Busch, U.; Ebner, T.; Schmid, J.; Lehmann, H.; Matzek, K.; Kemphorne-Rawson, J. A review on telmisartan: a novel, long-acting angiotensin II-receptor antagonist. *Cardiovasc. Drug Rev.* 2000, 18, 127−154.

(40) Yan, Y.-D.; Sung, J. H.; Kim, K. K.; Kim, D. W.; Kim, J. O.; Lee, B.-J.; Yong, C. S.; Choi, H.-G. Novel valsartan-loaded solid dispersion with enhanced bioavailability and no crystalline changes. *Int. J. Pharm.* 2012, 422, 202−210.

(41) Pharmacopeia, U. *National Formulary USP 38—NF 33*; United States Pharmacopeial Convention: Rockville, 2015.

(42) National Center for Biotechnology Information. Sodium carbonate$\text{Na}_2\text{CO}_3$—PubChem. PubChem Compound Database, 2018.

(43) Sengupta, P.; Chatterjee, B.; Pal, T. K. Assessment of preclinical pharmacokinetics and acute toxicity of pioglitazone and telmisartan combination. *Regul. Toxicol. Pharmacol.* 2017, 91, 151−158.

(44) Sengupta, P.; Chatterjee, B.; Mandal, U. K.; Gorain, B.; Pal, T. K. Development and validation of a high throughput LC−MS/MS method for simultaneous quantitation of pioglitazone and telmisartan in rat plasma and its application to a pharmacokinetic study. *J. Pharm. Anal.* 2017, 7, 381−387.