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SOLID STATE MANIPULATION OF TELMISARTAN *VIA* MECHANOCHEMICAL ACTIVATION WITH KAOLIN: AN ASSESSMENT OF BIOPHARMACEUTICAL PROPERTIES OF AMORPHOUS PHASE AND ITS PHYSICAL STABILITY

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Keywords:

Solid-state manipulation, Telmisartan, Mechanochemical activation, Kaolin, Amorphization, Dissolution enhancement

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ABSTRACT: The objective behind this study is to investigate the affinity between a carboxylic model drug telmisartan and kaolin. Telmisartan was comilled in solid state with kaolin in different weight ratios and characterized by Fourier transform infrared spectroscopy, Differential scanning calorimetry, X-ray powder diffractometry, scanning electron microscopy to examine the extent of transformation from crystalline to amorphous state. XRD and SEM studies revealed complete amorphization of telmisartan on comilling with kaolin for 1 h at 1:2 ratio. FTIR study showed that on milling with kaolin, the free acid carbonyl peak of telmisartan at 1692.14 cm^{-1} was disappeared, and a new carboxylate peak at 1578.72 cm^{-1} appeared. This disappearance of acid carbonyl peak and appearance of new carboxylate peak indicating an acid-base reaction between the carboxylic acid of telmisartan and kaolin. DSC study stated that in the milled samples, the melting endotherm of telmisartan was gradually shifted to lower temperature, and the intensity, as well as sharpness of the endotherm, was decreased. *In-vitro* study showed greater dissolution of telmisartan from telmisartan-kaolin milled powder as compared to pure drug. Stability study revealed that on storage also kaolin-telmisartan bound state was physically stable and the amorphous state of telmisartan in milled powder was unchanged.

INTRODUCTION: Low gastrointestinal solubility of an active pharmaceutical ingredient is the major problem for most of the drugs with respect to their oral bioavailability [1]. Solubility is very important for a drug because a drug in order to permeate through gastrointestinal barrier, should dissolve in the gastrointestinal fluid.

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Solubilization of poorly water-soluble APIs is one of the major challenges for screening studies of new chemical entities as well as in the fabrication of dosage form [2]. Several formulation strategies have been proposed to improve the solubility and dissolution rate of poorly water-soluble drugs by improving their amorphization, such as cosolvent addition, solvent evaporation, melt extrusion, spray drying, milling, *etc.* [3] Milling is a mechanical process commonly used for the reduction of particle size of drugs, modifies the surface properties such as surface area and porosity and helps to increase dissolution rates of poorly soluble drugs like progesterone and oxfendazole [4, 5].

A high level of mechanical energy was formed by this process, which generated sufficient strain in the solid particles. As a result, the solid particles were fractured and the crystal structure of the drug becomes altered [6]. Pressure, friction, attrition, and impact forces in ball milling are mainly responsible for the alteration of polymorphs and helps in the amorphization of drugs [7, 8]. Amorphization is an essential approach to improve the dissolution of drugs since the amorphous state is more readily soluble than its crystalline form due to higher Gibbs free energy [9].

Amorphization of the drug by compelling technique with adsorbents is one of the most explored fields in pharmaceutical research for the improvement of drug solubility as well as dissolution. This compelling technique is a relatively simple process that does not require sophisticated equipment, consumes less experimental time, easier scaling up, and, most importantly, non-utility of organic solvents [10, 11].

Telmisartan is an angiotensin-II receptor antagonist (ARB), indicated for the symptomatic management of hypertension. It is also used for the treatment of heart diseases, heart strokes, and bladder diseases. Telmisartan bind to the angiotensin II type one (AT1) receptors, inhibit the action of angiotensin II on vascular smooth muscle, and ultimately leading to a reduction in arterial blood pressure. Telmisartan is BCS Class II drug available in the free acid form and has very poor aqueous solubility i.e., 0.09 µg/ml [12].

As per the literature, several researchers have tried to improve the dissolution of telmisartan by incorporating it in solid dispersion [10], by mesoporous nanoparticles [13,] *etc*. Kaolin, a native hydrated aluminium silicate powder in nature, white to greyish-white in color and used as a good adsorbent [14]. It consists of microporous particles with a high specific surface area. It also contains silanol groups on its surface and is also used as a potential proton donor and acceptor.

In this present research, we emphasized the feasibility of using a ball mill to facilitate any physical or chemical interaction between kaolin and commercially available crystalline telmisartan in the solid-state. Telmisartan-kaolin compelled product was subjected to FTIR study to investigate the interactions between telmisartan and kaolin.

The prepared compelled powder was further subjected to scanning electron microscopy (SEM) and X-ray powder diffraction (XRD) study to monitor the conversion of crystalline telmisartan to its amorphous state. The influence of the drug/kaolin ratio on solubility and drug release was also examined. Finally, the physical stability of the prepared amorphous state of telmisartan was investigated by FTIR, DSC and XRD study.

MATERIALS AND METHODS:

Materials: Telmisartan (Carboxylic acid-containing crystalline powder), was a gift sample from Cipla Pvt. Ltd. Mumbai, India. Light kaolin (Hydrated aluminium silicate; white or yellowish-white powder with clay-like odour and taste) was obtained from Merck, India. It is insoluble in water, diluted acids as well as in alkali hydroxides.

Methods:

Solid State Milling: Solid-state milling of telmisartan was performed in a ball mill machine (Khera Pvt. Ltd., India) which consists of a cylindrical jar (inner diameter is 13.3 cm and inside capacity is 1 liter) and stainless steel balls. Before starting the milling process, the inner portion of the cylindrical jar and the balls were washed, cleaned, and dried properly. Then 50 nos. of balls (diameter is 1.15 cm) were placed in the jar and rotate at 100 rpm.

TABLE 1: FORMULATION CODE OF POWDERED SAMPLES OF TELMISARTAN CRYSTALLINE AND MILLED* WITH KAOLIN

Sample Code	Telmisartan (g)	Kaolin (g)	Telmisartan-Kaolin ratio	Status
TC	Crystalline	-	-	Unmilled
TM	Crystalline	-	-	Milled alone
$TK_{5:1}$	1	0.2	5:1	Comilled
$TK_{2:1}$	1	0.5	2:1	Comilled
$TK_{1:1}$	1	1	1:1	Comilled
$TK_{1:2}$	1	2	1:2	Comilled
$TK_{1:5}$	1	5	1:5	Comilled

*Milling was performed for 1 h at room temperature (~25°C).

The rotation of the cylindrical jar along with the balls allows significant attrition and impact on the powder sample. Pure crystalline telmisartan powder, as well as different ratio (weight basis) of telmisartan/kaolin, was placed in the ball mill machine **Table 1**. The milling operation was performed for 1 h at room temperature and no significant increase in temperature of the milled sample was detected at the end of the operation. Then the milled powder samples were sieved through mesh # 44 and kept in a desiccator for further analysis. The extent of amorphization was examined by evaluating them for drug crystallinity using Scanning Electron Microscopy and XRD. The interaction of the telmisartan with kaolin was confirmed by FTIR and DSC studies.

Physicochemical Characterization:

Measurement of Solubility: Solubility studies of pure telmisartan, telmisartan milled alone sample and different ratio of telmisartan/kaolin samples were performed by adding excess amount of sample in 100 ml of phosphate buffer (pH 6.8) and stirred it for 6 hours using a magnetic stirrer. Then the solution was sonicated (Imeco Sonifier, Imeco Ultrasonics, India) at 125 W for 15 min. Then the solution was filtered and subjected to spectrophotometric analysis at 296 nm using UV-visible spectrophotometer (UV-1800 Shimadzu. Japan). Each determination was made in triplicate and shown in **Table 2**.

Melting Point Determination: Melting point of pure telmisartan crystal, telmisartan milled without kaolin and telmisartan-kaolin powder blend of different ratio was determined by the capillary method. Fine powder samples were filled in capillary tube (previously sealed at one end). The capillary tube was then inserted in the sample holder of the melting point apparatus and a thermometer was also placed in the apparatus. The temperature at which powder samples melted was noticed and shown in **Table 2**.

Fourier Transform Infrared (FTIR) Spectroscopy: FTIR spectra of pure telmisartan crystal, telmisartan milled without kaolin, and telmisartan-kaolin powder blends were obtained using FTIR analyzer (Prestige-21, Shimadzu FT-IR, Japan). The pellets of all the samples with KBr were prepared on KBr-pellet press (Kimaya Engineers, India) under hydraulic pressure of 5 Ton. The samples were scanned over a wavenumber range between 4000 to 500 cm^{-1} at room temperature.

Thermal Analysis: Differential scanning calorimetry (DSC) analysis of pure telmisartan crystal, telmisartan milled without kaolin, and telmisartan-kaolin powder blends were performed by using Differential Scanning Calorimeter (Diamond DSC, PYRIS, Perkin Elmer, USA). Indium standard was used to calibrate the DSC temperature and enthalpy scale. The samples were hermetically sealed in perforated aluminum pans and heated at a constant rate of 10 °C/min over a temperature range of 50 °C to 400 °C. The system was purged with nitrogen gas at the rate of 100 mL/min to maintain an inert atmosphere.

Solid-State Characterization:

X-Ray Powder Diffraction (XRPD) Studies: Samples of pure telmisartan crystal, telmisartan milled without kaolin, and telmisartan-kaolin powder blends were assessed for crystallinity by using X-ray diffractometer (Xpert Pro Multi-Purpose Diffractometer, PANAlytical, Netherlands) using monochromatized Cu Kα radiation (λ = 1.54 Å) at a voltage of 45 kV and current of 40 mA. Measurements were carried out in the angular scan range from 5° to 60° (2θ) at a scan speed of 2°/min.

Scanning Electron Microscopy (SEM): Pure telmisartan crystal, telmisartan milled without kaolin, and telmisartan-kaolin powder blends were assessed for crystallinity by using scanning electron microscope (S 3700 VP FE-SEM, Hitachi High-Technologies, Europe). The samples were mounted on an aluminum stab using adhesive tape and coated for 120 s with a layer of gold using a sputter coater. Then the stub-containing sample was placed in a scanning electron microscope chamber at an acceleration voltage of 17 kV and a pressure of 0.6 mm Hg. Then the photographs of samples were taken using a scanning electron microscope.

***In-vitro* Dissolution Studies:** *In-vitro* dissolution study was performed by using USP dissolution rate test apparatus II (DISSO 8000, LAB INDIA, India) at 100 rpm. An accurately weighed quantity of sample was placed in a dissolution flask containing 900 ml of phosphate buffer (pH 6.8). At each predetermined time interval, a 5 ml sample was

withdrawn from the dissolution vessel, filtered through Whatman filter paper, and replaced with an equal amount of fresh dissolution medium to maintain the sink condition. The sample of each time interval was suitably diluted, and the drug content in the withdrawn aliquots was analyzed spectrophotometrically at 296 nm using UV-visible spectrophotometer (UV-2450, Shimadzu. Japan).

Stability Studies: The milled powder $TK_{1:2}$ was stored at 40 ± 2 °C; 75 ± 5 % RH for six months. After six months, FTIR spectra, DSC spectra, and XRD spectra were performed to examine any interaction and evaluate any changes in drug crystallinity. *In-vitro* drug release was also performed and statistically investigated to observe any possible changes in drug release during storage.

RESULTS AND DISCUSSION: Pure telmisartan in its solid-state was milled with a ball mill machine in the presence as well as in the absence of kaolin to examine whether the amorphization of telmisartan was possible upon ball milling with kaolin or not. It was observed that without kaolin there was no alteration in telmisartan crystallinity after milling it for 1 h whereas significant changes were observed after milling with kaolin. Gupta *et al.*, 2003 observed no alteration of drug crystallinity when ketoprofen, naproxen and indomethacin were milled alone for 48 h at 25 °C and 40% RH [5]. In this present research, ball mill operation was performed at laboratory ambient temperature (*i.e.*, 25 °C) because if the alteration in drug crystallinity after milling with kaolin could be possible, then this process would be scalable and used for commercial purposes.

Physicochemical Characterization:

Measurement of Solubility: Solubility analysis of telmisartan crystal (TC), telmisartan milled without kaolin (TM), and telmisartan-kaolin blends is shown in **Table 2**. Solubility analysis revealed that telmisartan crystal (TC) showed 5.21 ± 1.04 µg/ml solubility in distilled water at 37 °C. When telmisartan was milled without kaolin for 1h, the solubility of telmisartan was very slightly improved (7.11 ± 1.21 µg/ml). This may be due to the fact that when the pure drug was milled alone, its particle size was reduced as well as surface area was increased. As a result, the contact between pure drug and solvent was also increased, which improve the solubility of pure drug. It was also observed that when telmisartan was milled with kaolin a significant improvement in solubility of pure drug was noticed. The maximum solubility was observed in $TK_{1:2}$ sample of about 67.89 ± 2.53 µg/ml. This improvement in solubility suggests that when telmisartan was milled with kaolin it may convert to amorphous state from its crystalline state. The increased in solubility may be due to the disordered structure of the amorphous solid as well as due to the intermolecular interactions in the prepared amorphous system no lattice energy has to be overcome [15]. This helps to increase the solubility of the milled samples. Therefore solubility of telmisartan from the samples are in the order as: $TC < TM < TK_{5:1} < TK_{1:5} < TK_{2:1} < TK_{1:1} < TK_{1:2}$.

TABLE 2: PHYSICO-CHEMICAL CHARACTERIZATION OF TELMISARTAN CRYSTAL (TC), TELMISARTAN MILLED ALONE (TM) AND TELMISARTAN-KAOLIN BLENDS

Sample Code	Solubility (µg/ml)	Melting point
TC	5.21 ± 1.04	270 ± 3 °C
TM	7.11 ± 1.21	267 ± 4 °C
$TK_{5:1}$	18.61 ± 2.51	259 ± 3 °C
$TK_{2:1}$	39.58 ± 1.89	213 ± 2 °C
$TK_{1:1}$	51.52 ± 3.04	191 ± 3 °C
$TK_{1:2}$	67.89 ± 2.53	168 ± 4 °C
$TK_{1:5}$	27.74 ± 2.96	243 ± 3 °C

Mean ± SD., n=3

Melting Point Determination: Melting point of telmisartan crystal (TC), telmisartan milled without kaolin (TM) and telmisartan-kaolin blends is shown in **Table 2**. This study revealed that telmisartan crystal (TC) showed its melting point at 270 ± 3 °C whereas when telmisartan crystals were milled alone (TM) (without kaolin), its showed its melting point at 267 ± 4 °C. But there was a significant changes in melting point was noticed when telmisartan was milled with different ratio of kaolin. Among all the telmisartan-kaolin blends 1:1 and 1:2 ratio showed maximum decrease in melting point *i.e.* 191 ± 3 °C and 168 ± 4 °C respectively. This may be due to the fact that in the milled telmisartan-kaolin sample, crystalline telmisartan was converted to amorphous state. So it was concluded from the melting point study that crystalline telmisartan was converted to amorphous form when milled with kaolin for 1 h.

Fourier Transform Infrared (FTIR) Spectroscopy: The interaction of drug and carrier can lead to changes in bonding between functional groups can be detected by FTIR spectroscopy [16, 17]. The FTIR spectra of pure telmisartan crystal, telmisartan milled without kaolin and telmisartan-kaolin powder blends are shown in **Fig. 1**. FTIR spectra revealed that in pure telmisartan crystal free acid carbonyl peak was present at 1692.14 cm^{-1}. In the TM sample (telmisartan milled without kaolin) no significant changes were observed in the peak characteristics when compared with pure telmisartan crystal (TC) whereas in the milled powder blends the free acid carbonyl peak was very weak and gradually disappeared as a function of drug/kaolin ratio. In the milled samples, a new peak was observed at 1578.72 cm^{-1} which denotes the arrival of new carboxylate ion in the milled powder blends. As a function of drug/kaolin ratio, a reduction in absorbance of the free acid carbonyl peak as well as a corresponding increase in the absorbance of carboxylate peak was observed. This interaction may be due to the acid-base interaction between the carboxylic acid group of telmisartan and Al_2O_3 of kaolin.

This acid-base reaction plays an important role in alterations in the FTIR spectra of milled powders. In this reaction the free acid carboxyl peak was converted to carboxylate ion. As per the literature carboxylate ion shows a strong peak in the region 1540 cm^{-1} to 1650 cm^{-1} [18]. From Fig. 1 it was clear that in the milled samples the absorbance of drug free acid carboxyl peak was gradually decreased and absorbance of new carboxylate ion peak was increase. The same finding was observed with the storage milled powder. The changes in the FTIR spectra are supposed to indicate an acid-base interaction between the carboxylic acid of telmisartan and Al_2O_3 of kaolin to form its salt.

Kararli et al., 1989 examined solid state interaction between magnesium oxide and ibuprofen and observed the formation of the magnesium salt of ibuprofen by an acid-base reaction between magnesium oxide and ibuprofen [19]. In this present research disappearance of the carbonyl peak (1692.14 cm^{-1}) and reappearance of the carboxylate peak (1578.72 cm^{-1}) in the milled samples suggested the conversion of crystalline telmisartan to amorphous salt of telmisartan.

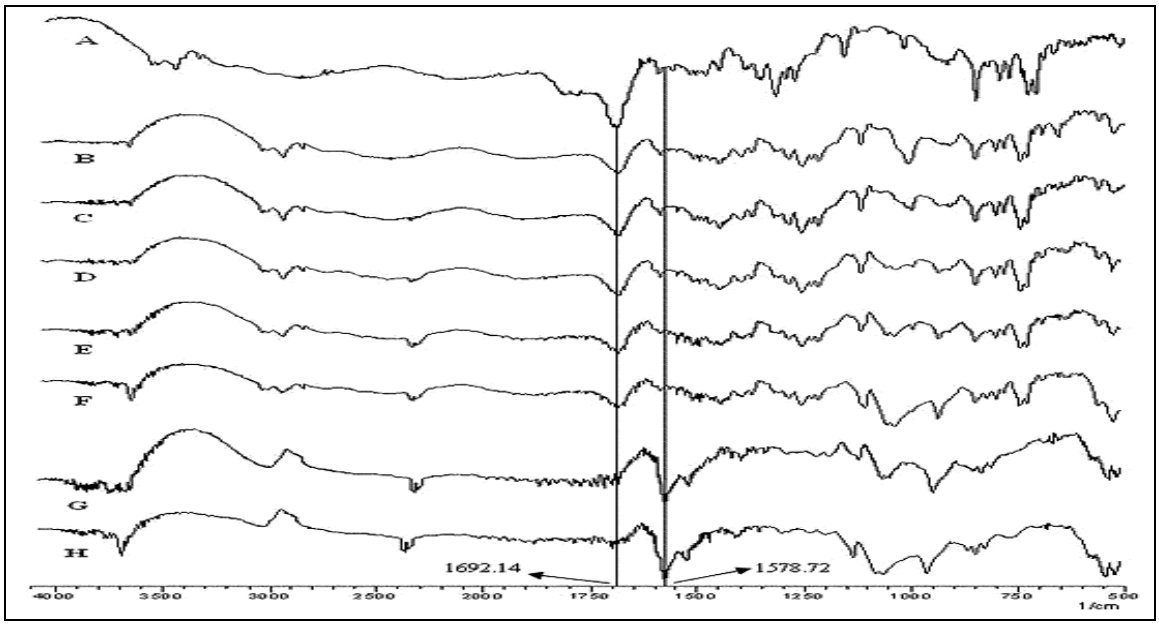

FIG. 1: FTIR SPECTRA OF PURE TELMISARTAN CRYSTAL AND TELMISARTAN MILLED SAMPLES FOR 1 h WITHOUT AND WITH KAOLIN AT DIFFERENT PROPORTIONS. A=TC; B=TM; C= $TK_{5:1}$; D= $TK_{2:1}$; E= $TK_{1:5}$; F= $TK_{1:1}$; G= $TK_{1:2}$; H= $TK_{1:2}$ (6 MONTHS/40 °C/ 75% RH)

Tong *et al.*, 2002 examined the electrostatic interactions between alkali metal counter ions and indomethacin and reported the formation of higher physically stable salt form of indomethacin in comparison with its acid form due to stronger electrostatic interactions between the carboxylate group of indomethacin and counter ions at glass transition temperature [18]. In this present research the conversion of crystalline telmisartan to its amorphous state may also due to the hydrogen

bonding interactions as well as electrostatic interactions between COO^- and counter ion Al^{3+}. Disappearance of the carboxylic acid peak and reappearance of the carboxylate peak in the FTIR spectra of telmisartan milled with kaolin suggest amorphous salt formation in the present study. The conversion of crystalline form to amorphous state of telmisartan was further confirmed with XRD and SEM study.

Thermal Analysis: The physicochemical state of pure telmisartan crystal, telmisartan milled without kaolin and telmisartan-kaolin powder blends was assessed by Differential Scanning Calorimetric analysis and shown in **Fig. 2**. DSC thermogram of pure telmisartan (TC) exhibited a single sharp endothermal at 272.51 °C, corresponding to its melting point. In the TM sample (telmisartan milled without kaolin) no significant changes were observed in melting endotherm (264.20 °C) when compared with pure telmisartan crystal whereas in the milled powder blends, the intense of pure telmisartan endothermal peak decreased. In the milled samples, the melting endotherm of telmisartan was gradually shifted to a lower temperature, and the intensity, as well as the sharpness of the endotherm, was decreased. Among all the drug/kaolin ratio, $TK_{1:2}$ sample showed the maximum amorphization of telmisartan compared to other samples. $TK_{1:2}$ sample exhibited a broad endothermic peak at 172.27 °C, corresponding to telmisartan melting point. This may be due to the fact that in the milled telmisartan-kaolin sample, crystalline telmisartan was converted to an amorphous state. The amorphization of telmisartan in the milled samples was further confirmed by XRD and SEM study.

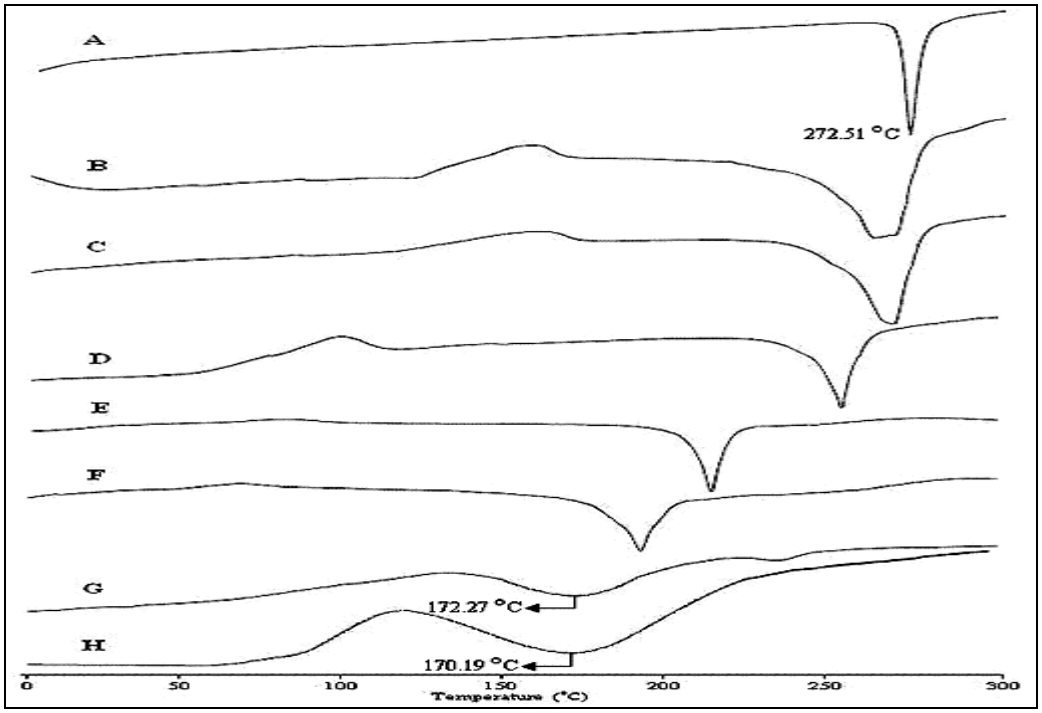

FIG. 2: DSC CURVES OF PURE TELMISARTAN CRYSTAL AND TELMISARTAN MILLED SAMPLES FOR 1 H WITH KAOLIN AT DIFFERENT PROPORTIONS. A=TC; B=TM; C= $TK_{5:1}$; D= $TK_{2:1}$; E= $TK_{1:5}$; F= $TK_{1:1}$; G= $TK_{1:2}$; H= $TK_{1:2}$ (6 MONTHS/40 °C/ 75% RH)

Solid-State Characterization:

X-Ray Powder Diffraction (XRPD) Studies: X-ray diffraction pattern of pure telmisartan crystal, telmisartan milled without kaolin and telmisartan-kaolin powder blends are shown in **Fig. 3**. The pure telmisartan (A) exhibited sharp diffraction peaks at 2θ values of 6.24°, 14.06°, 14.93°, 16.17°, 18.02°, 20.16°, 21.37°, 22.09°, 25.27°, *etc*.

The XRD pattern of kaolin (H) showed major diffraction peaks at 2θ values of 12.79°, 25.27° and 28.49°. In case of telmisartan milled alone sample (B), no significant difference with respect to the diffraction peaks were observed as compared to crystalline telmisartan. It is extremely important to note that without kaolin the API did not become amorphous.

These data demonstrate the importance of adding kaolin to obtain amorphous telmisartan. The XRD pattern of $TK_{1:1}$ and $TK_{1:2}$ did not show the sharp diffraction peaks of telmisartan as it was shown in $TK_{5:1}$, $TK_{1:5,}$ and $TK_{2:1}$ which concluded that with $TK_{1:1}$ and $TK_{1:2}$ samples, complete amorphization of telmisartan was taken place.

This amorphization of telmisartan explaining the significant increase in solubility of the API in $TK_{1:1}$ and $TK_{1:2}$. The increase in solubility may be due to the disordered structure of the amorphous solid. To dissolve any crystalline substance, it is very much important to disrupt the lattice, whereas to dissolve any amorphous system, no disruption of the lattice is required as well as no lattice energy has to be overcome to dissolve the amorphous substance [20].

So the XRD study of different drug-kaolin blends revealed the reduced ordering of crystal lattice of telmisartan as the following: TC > TM > $TK_{5:1}$ > $TK_{1:5}$ > $TK_{2:1}$ > $TK_{1:1}$ > $TK_{1:2}$.

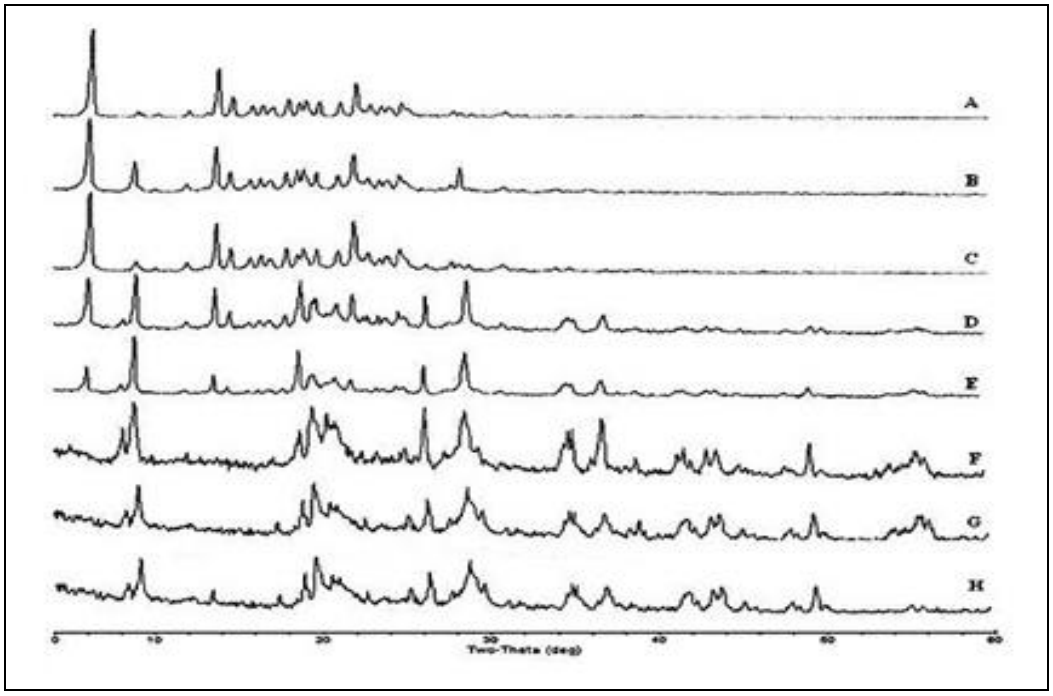

FIG. 3: X-RAY POWDER DIFFRACTION PATTERNS OF PURE TELMISARTAN CRYSTAL AND TELMISARTAN MILLED SAMPLES FOR 1 H WITH KAOLIN AT DIFFERENT PROPORTIONS. A=TC; B=TM; C= $TK_{5:1}$; D= $TK_{2:1}$; E= $TK_{1:5}$; F= $TK_{1:1}$; G= $TK_{1:2}$; H= $TK_{1:2}$ (6 MONTHS/40 °C/ 75% RH)

Scanning Electron Microscopy (SEM): Ball milled samples of telmisartan were subjected to SEM study to determine the extent of amorphization of telmisartan.

This study revealed sharp needle-like geometric shapes of pure telmisartan (TC) due to its crystalline nature in the pure form **Fig. 4A**. When telmisartan was milled alone without kaolin (TM), no significant changes were observed in its needle-like morphology as well as telmisartan crystal geometry **Fig. 4B**.

On milling with kaolin, the particle size of telmisartan was reduced as well as distinctive needle-like morphological view and geometric shape has gradually disappeared as kaolin concentration was increased.

SEM study showed that telmisartan crystals were not completely disappeared in the milled sample of $TK_{1:1}$ **Fig. 4B**. On increasing the kaolin concentration in sample $TK_{1:2}$ **Fig. 4D**, moist agglomerate particles were formed in which telmisartan crystals were not at all identified, which revealed almost complete disappearance of crystal morphology (loss of geometric shape of crystal).

So SEM study concluded that the formation of the amorphous state of telmisartan is feasible by ball milling with kaolin, whereas amorphization does not occur on milling the drug alone.

The carboxylic acid-containing telmisartan showed almost complete amorphization on milling with kaolin ($TK_{1:2}$).

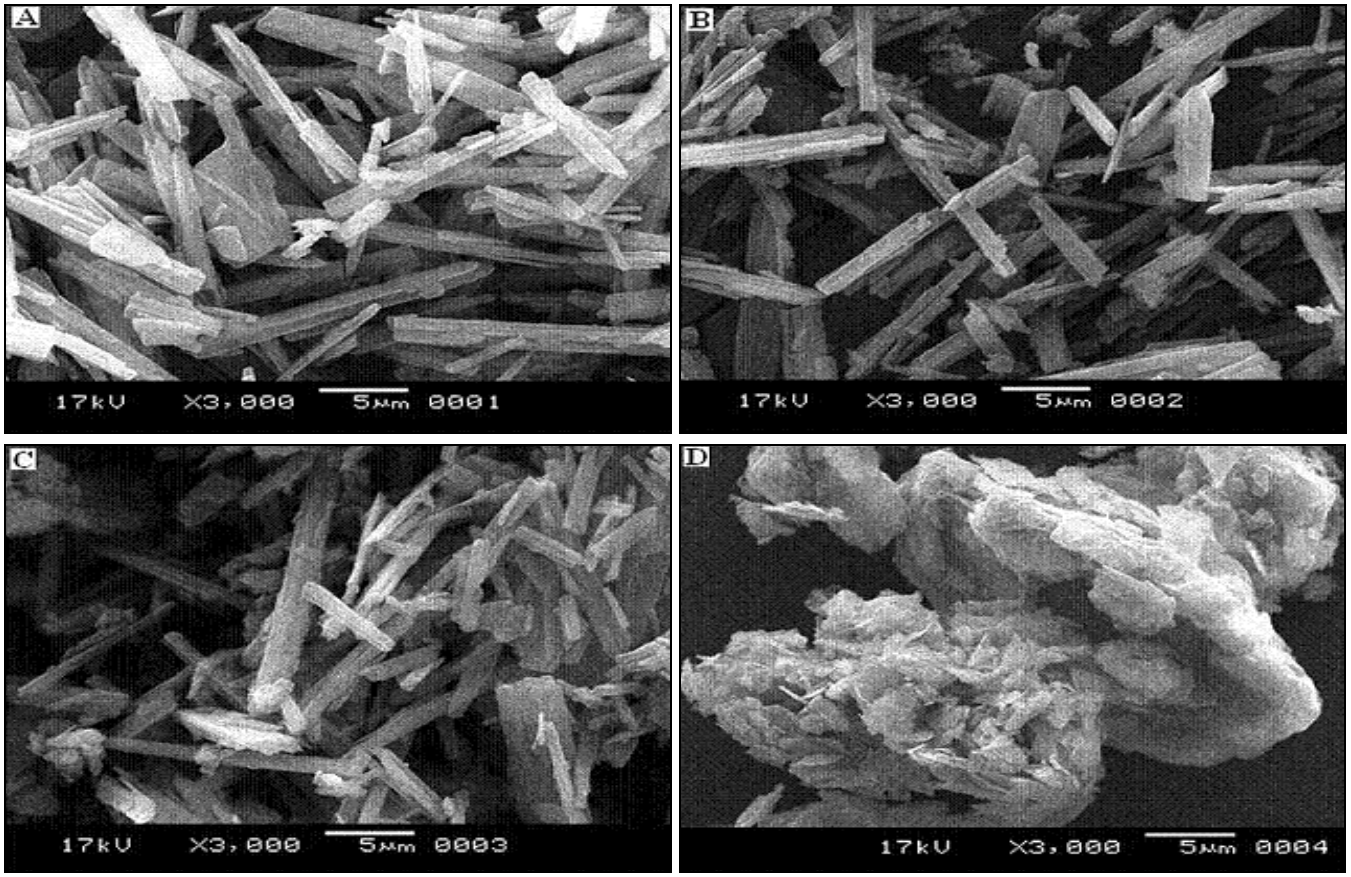

FIG. 4: SEM PHOTOGRAPHS OF TELMISARTAN CRYSTAL (TC) (A), TELMISARTAN MILLED WITHOUT KAOLIN (TM) (B), TELMISARTAN MILLED WITH KAOLIN ($TK_{1:1}$) (C) AND TELMISARTAN-KAOLIN OPTIMIZED POWDER MILLED ($TK_{1:2}$) (D). MAGNIFICATION 3000x

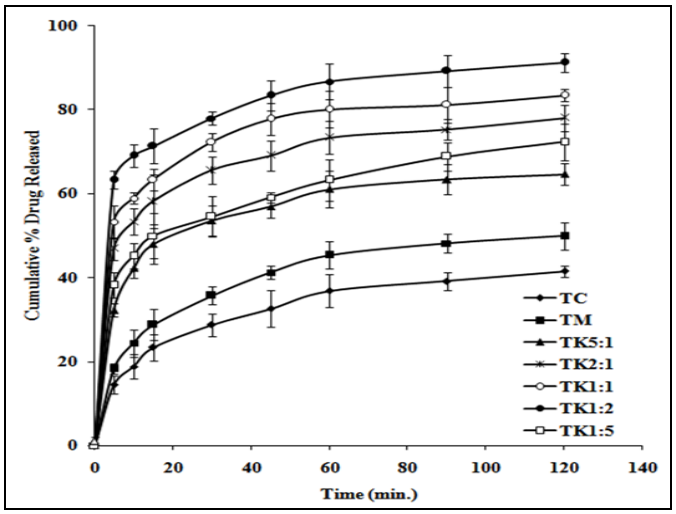

FIG. 5: CUMULATIVE PERCENTAGE OF TELMISARTAN RELEASED IN *IN-VITRO* DISSOLUTION STUDIES FROM SAMPLES OF TELMISARTAN CRYSTAL AND TELMI-SARTAN MILLED SAMPLES FOR 1 H WITH KAOLIN AT DIFFERENT PROPORTIONS. Each point represents mean ± SD, n = 3. Sample $TK_{1:2}$ showed a significantly greater dissolution rate as compared to all other samples ($p < 0.05$)

***In-vitro* Dissolution Studies:** *In-vitro* drug release profiles from telmisartan crystalline (TC), telmisartan milled without kaolin (TM) and different ratios of telmisartan-kaolin powder blends are shown in **Fig. 5**. In the case of telmisartan crystal (TC), only 41.47 ± 1.36 % drug was release, whereas from telmisartan milled alone sample (TM), 49.83 ± 3.27 % drug was released within 120 min. Slightly increased values of percent drug release were found from telmisartan milled alone sample than telmisartan crystalline sample. This may be due to the fact that the milling process increases the effective surface area of telmisartan drug particles which exhibited slightly increased dissolution than the unmilled drug.

When telmisartan was milled with kaolin showed greater dissolution compared with both telmisartan crystalline form and telmisartan milled alone sample. It was observed that the percent release of telmisartan increased gradually with the gradual increase in kaolin proportion in the milled powders. The formulation $TK_{1:2}$ exhibited the greatest percentage of drug release, *i.e.*, 91.10 ± 2.15% among all the formulations. These observations suggest that when telmisartan was milled with kaolin, the crystalline form of telmisartan was converted to amorphous form and the crystal lattice

of crystalline telmisartan was gradually reduced [21]. These results also indicate that the improvement of this biopharmaceutical property was dependent on the drug: kaolin ratio. Further increase in kaolin concentration (formulation $TK_{1:5}$), decreased drug release was observed (*i.e.*, 72.19 ± 4.35 %). This may be due to the chemical interaction between drug and kaolin. At higher concentrations, kaolin forms a very stable complex with the carboxyl group of telmisartan which is also not easily soluble and decreased the drug release. Cumulative percent release of telmisartan from the formulations are in the order as: TC < TM < $TK_{5:1}$ < $TK_{1:5}$ < $TK_{2:1}$ < $TK_{1:1}$ < $TK_{1:2}$.

Stability Studies: The formulation $TK_{1:2}$ was stored at 40 ± 2 °C and 75 ± 5 % RH for six months, and after six months, it was examined by FTIR, DSC, and XRD for any changes in telmisartan-kaolin interaction and drug crystallinity. It is reported that thermodynamically unstable systems such as amorphous systems always have a tendency to undergo recrystallization to their more stable state at any moment [22]. However, literature also demonstrated that the presence of hydrophilic carriers inhibits the recrystallization of amorphous drugs [23, 24]. So it is very much essential to perform the stability study of the prepared amorphous system.

In-vitro drug release was also performed and statistically investigated to observe any possible changes in drug release during storage **Fig. 6**. The morphological evaluation suggested the stable nature of formulation $TK_{1:2,}$ and no changes were observed with respect to its colour and odour. FTIR spectra **Fig. 1H** suggested that the free acid carbonyl peak of pure telmisartan crystal did not reappear on storage of the sample, and the presence of carboxylate peak of the same sample did not disappear after storage. FTIR spectra confirmed that after storage also the amorphous state of telmisartan in formulation $TK_{1:2}$ was not converted to its crystalline form. These results indicating the maintenance of the initial interactions between the telmisartan and kaolin. FTIR data suggest that the formulations remained stable under this condition. DSC study suggested that the broad endothermic peak of the formulation $TK_{1:2}$ did not disappear after storing but shifted slightly from 172.27 °C to 170.19 °C **Fig. 3H** and confirmed that the amorphous state of telmisartan was remaining unchanged. XRD study stated that there was no significant difference in the peaks of the stored sample and confirmed that the absence of any significant reversion from an amorphous state to the crystalline state. *In-vitro* drug release study suggested no significant difference in drug release of the stored sample **Fig. 6**.

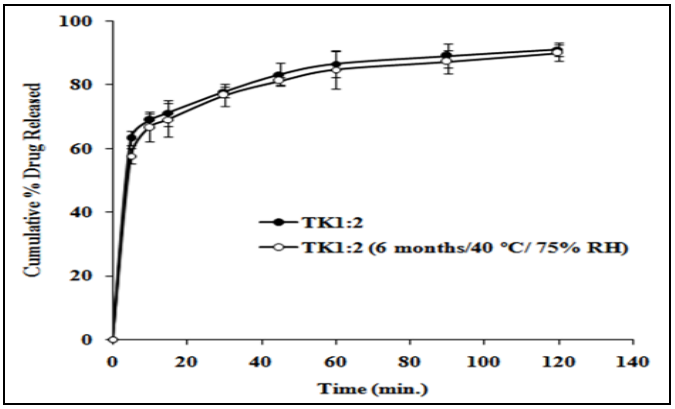

FIG. 6: CUMULATIVE PERCENTAGE OF TELMISARTAN RELEASED IN *IN-VITRO* DISSOLUTION STUDIES FROM OPTIMIZED TELMISARTAN-KAOLIN MILLED SAMPLE AND OPTIMIZED TELMISARTAN-KAOLIN MILLED SAMPLE AFTER SIX MONTHS OF STABILITY STUDY. Each point represents mean ± SD, n = 3. Sample $TK_{1:2}$ and $TK_{1:2}$ (6 months/40 °C/ 75% RH) showed no significant difference in drug release ($p < 0.05$)

CONCLUSION: In this present research, we emphasized the feasibility of using a ball mill to facilitate the possible physical or chemical interaction between kaolin and commercially available crystalline telmisartan in the solid-state. The improvement in solubility suggested that when crystalline telmisartan was milled with kaolin it may convert to its amorphous state. SEM and XRD studies revealed the amorphous state of telmisartan upon ball milling with kaolin. The disappearance of carboxylic acid peak and reappearance of carboxylate peak in the FTIR spectra suggested amorphous salt formation of telmisartan. Dissolution study revealed that when telmisartan-kaolin milled samples showed greater dissolution as compared with both telmisartan crystalline form as well as telmisartan milled alone sample. Stability study confirmed the physically stable nature of telmisartan-kaolin milled sample on storage at 40 °C and 75% RH for six months. So the present research concluded that the biopharmaceutical properties of telmisartan largely depend on the mechanochemical activation and concentration of kaolin.

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