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DEVELOPMENT AND CHARACTERIZATION OF TELMISARTAN TABLET BY THE USE OF CO-CRYSTALLIZATION TECHNIQUE

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ABSTRACT

Telmisartan is an angiotensin II receptor antagonist (angiotensin receptor blocker, ARB) used in the management of hypertension. Telmisartan belongs to class II drug in BCS classification i.e. low solubility and high permeability. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. The purpose of this study was to prepare pharmaceutical co-crystals of Telmisartan to enhance solubility and dissolution rate of Telmisartan. Co-crystallization is an effective crystal engineering approach for modifying the crystal structure and properties of drugs. Pharmaceutical co-crystals are nonionic supramolecular complexes and can be used to altered physical property issues such as solubility, stability and bioavailability in pharmaceutical development without affecting chemical composition of API. Co-crystallization can improve physiochemical properties like solubility, dissolution rate, chemical stability and melting point.

KEYWORDS: Co-crystals, Telmisartan, Co-former, Solubility, Invitro-Dissolution.

INTRODUCTION

Co-crystals can be defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non covalent interactions (primarily hydrogen bonding). The formation of pharmaceutical co-crystals involves incorporation of a given API with another pharmaceutically acceptable molecule in the crystal lattice. The resulting multi-component crystalline phase will maintain the intrinsic activity of the parent API. The key benefits associated with co crystallization approach to modifying properties of pharmaceutical solids including weakly ionizable and non-ionizable, to form co crystals, and

the existence of numerous potential counter-molecules, including food additives, preservatives, pharmaceutical excipients as well as other APIs, for co-crystal synthesis.[1]

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.[2] Some conventional methods used to improve aqueous solubility and bioavailability include: the use of surfactants, pH modification, solid dispersion technique, co-solvent and hydrotrop formation, particle size reduction, pro-drugs and many more.[3-5]

Conventional methods may not always lead to success in some cases and new methods are occasionally introduced. Under these circumstances, improvement of physicochemical properties of a poorly soluble API necessitates the need for alternative strategies such as crystal engineering and recently pharmaceutical co-crystals have been proposed as a unique crystal engineering opportunity to alter the physicochemical properties of compounds.[6-7]

According to FDA guidance that was recently released on pharmaceutical co-crystals[8], they are defined as "Crystalline materials composed of two or more molecules within the same crystal lattice." Co-crystallization is a result of competing molecular associations between similar molecules or homomers and different molecules or heteromers. The components in a co-crystal exist in a definite stoichiometric ratio, and assemble via non-covalent interactions such as hydrogen bonds, ionic bonds, π-π or Van der Waals interactions rather than by ion pairing.[9]

Telmisartan is an angiotensin II receptor antagonist (angiotensin receptor blocker, ARB) used in the management of hypertension. According to BCS, Telmisartan is classified as a low solubility and high permeability drug (class II). [10] Therefore, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. The purpose of this study was to prepare pharmaceutical co-crystals of Telmisartan to enhance solubility and dissolution rate of Telmisartan.

MATERIALS AND METHODS

Materials

Telmisartan was received as a gift sample from Yarrow Chem Products, Mumbai, India. Benzoic Acid, Salisylic Acid, Cinnamic Acid, Acetyl Salicylic Acid, Tartaric Acid, Pthalic

Acid, Citric Acid were received from Zim Leboratory, Kalmeshwar MIDC, Nagpur, India. All other materials used were of pharmaceutical or analytical grade.

Preparation of Co-Crystals

Neat Grinding method: In this neat grinding technique where the materials were mixed, pressed and crushed in a mortar and pestle. The pure drug and all co-factors in various ratios 20 mg:80 mg, 40 mg:60 mg, 50 mg:50 mg, 60 mg:40 mg, 20 mg:80 mg were mixed and crushed in a mortar & pestle for ½ hour and stored in zip-lock pouches for further study.

Screening of Co-Factor[15]

The screening of co-factors was performed by comparing the solubility of pure drug with different co-factors (Different Acids) in different concentration ratios 20 mg: 80 mg, 40 mg: 60 mg, 50 mg:50 mg(1:1), 60 mg:40 mg, 20 mg:80 mg. For each preparation, an equivalent of 10 mg of drug was added to each media in glass vials with caps. The vials were kept on an Orbital Shaking incubator maintained at 37 ± 0.5 °C for 24 h. After that the solution was centrifuged and filtered. The filtrate was suitably diluted with distilled water and analyzed using a UV spectrophotometer at 291 nm.

Table No. 1: List of Co-factors used with their codes.

Sr. No.	Batch	Names of Co-factor
1	A	Benzoic Acid
2	B	Salicylic Acid
3	C	Cinnamic Acid
4	D	Tartaric Acid
5	E	Phthalic Acid
6	F	Sulfanilic Acid
7	G	Acetyl Salicylic Acid
8	H	Citric Acid

EVALUATION OF SELECTED TELMISARTAN CO-CRYSTALS

Melting point determination[12]

The melting point was determined by the capillary method. In this methodology, a thin glass capillary tube containing a substance to be determined was introduced into a heated stand (liquid paraffin bath called Thiel's Tube) in close proximity to a high accuracy thermometer. The temperature in the heating stand was raised at a fixed rate until the sample in the tube transitioned into the liquid state.

Light Microscopy[13]

Light microscopy has been utilized to examine the particle size of co-crystals of selected batches. The size of the co-crystals can be characterized with stage micrometer and eye piece micrometer. The eye piece micrometer was calibrated stage micrometer. The sizes around 100 particles were measured and their average particle size determine.

Solubility study[16]

1. In Distilled Water

The solubility of Telmisartan and co-crystals using Stoichiometric ratios were determined in distilled water. For each preparation, an equivalent of 20 mg of drug was added to each media in glass vials with caps. The vials were kept on an Orbital Shaking incubator (REMI ELEKTROTECHNIK LIMITED, Vashi, India) maintained at 37 ± 0.5 °C for 24 h. After that the solution was centrifuged and filtered. The filtrate was suitably diluted with distilled water and filtrate was analyzed using a double beam UV spectrophotometer (UV-1800; Shimadzu, Kyoto, Japan) at 291 nm.

2. In 0.1N HCl

The solubility of Telmisartan and co-crystals using Stoichiometric ratios were determined in 0.1N HCl. For each preparation, an equivalent of 20 mg of drug was added to each media in glass vials with caps. The vials were kept on an Orbital Shaking incubator (REMI ELEKTROTECHNIK LIMITED, Vashi, India) maintained at 37 ± 0.5 °C for 24 h. After that the solution was centrifuged and filtered. The filtrate was suitably diluted with 0.1 N HCl and filtrate was analyzed using UV spectrophotometer (UV-1800; Shimadzu, Kyoto, Japan) at 224 nm.

In vitro dissolution study[17-18]

The in vitro dissolution study was performed using USP apparatus type II (TDT-08T, Electrolab, Mumbai, India) fitted with paddle (50 rpm) at 37±0.5^{0}C using Distilled Water as a dissolution medium. At the predetermined time intervals (10, 20, 30, 45, 60, 90 and 120 min), 5 ml samples were withdrawn, filtered and assayed at 291 nm using Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). At each time point, withdrawn volume was replaced with fresh dissolution media. Cumulative percentage drug release was calculated using an equation obtained from a calibration curve.

Fourier Transform Infrared Spectroscopy[19]

FTIR spectra of Telmisartan and optimized batch of co-crystals were obtained on a FTIR-8400S (Shimadzu, Tokyo, Japan) using the KBr disk method. The scanning range was 4000–500 cm^{-1}.

Powder X-ray diffraction[20]

Powder X-ray diffraction pattern of Telmisartan and optimized batch of co-crystals were recorded using a diffractometer (PW 1140, Mettler Toledo, Columbus, USA) and Cu-kα radiation. The diffractometer was run at a scanning speed of 2^0/min and a chart speed of 2^0/2 cm per 2θ.

Preparation of Tablet of Optimized Co-Crystals[21]

Conventional tablets of optimized co-crystal batch C4 were prepared by Wet Granulation Technique.

Wet Granulation Method: Wet granulation forms the granules by binding the powders together with an adhesive, instead of by compaction. Formulation layout of optimized co-crystals tablet is shown in table no.02. The all weighed ingredients mixed together and triturated well in mortal & pestle. Isopropyl alcohol (IPA) was used as solvent in ratio 8:2 with water. Drop by drop solvent was added to the triturated mixture and a partially solid blend was obtained. Then this blend was rubbed on sieve no. 10 and the obtained granules were allowed to dry at room temperature. The dried granules were used for tablet punching.

Table 02: Formulation layout of tablet of optimized co-crystals.

Sr. No.	Ingredients	Quantity for each Tablet (mg)
1	Optimized co-crystals (1:4)	200
2	Micro Crystalline Cellulose	25
3	Talc	6.25
4	Magnesium Stearate	6.25
5	Lactose	12.5
6	**Total**	**250**

EVALUATION OF TABLETS

A. Pre-Compression Evaluations[21]

The prepared granules of co-crystals were evaluated for various pre-compression parameters like,

Bulk Density

A quantity of accurately weighed powder (bulk) was introduced into a 100 ml measuring cylinder. Noticed the volume covered by the powder in the cylinder i.e. height of the bulk. And the bulk density was calculated by following formula;

$$\text{Bulk Density} = \frac{\text{Mass of Co-crystals}}{\text{Bulk Volume}}$$

Tapped Density

A quantity of accurately weighed powder (bulk) from each formula, previously shaken to break any agglomerates formed was introduced into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5cm at 2 sec interval. The taping was continued until no further change in volume was noted. And the tapped density was calculated by following formula;

$$\text{Tapped Density} = \frac{\text{Mass of Co-crystals}}{\text{Tapped Volume}}$$

Carr's Index

Carr's Index was calculated with the help of bulk and tapped density by using following formula and result was shown in Table No. 8.

$$\text{Carr's Index} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100$$

Hausner Index

Hausner Ratio was calculated with the help of bulk and tapped density by using following formula and result was shown in Table No. 8.

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Angle of Repose

A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, there by evaluating the flow ability of the granules. Height of the pile was also measured.

$$\Theta = \tan^{-1} (h/r)$$

Where, Θ is the angle of repose;

h is the height;

r is the radius.

B. Post-compression Evaluations[22]

The prepared tablets of co-crystals were evaluated for various post-compression parameters like,

Hardness Test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the same tablets from each formulation was determined. The mean and standard deviation values were also calculated.

Weight Variation Test

The weight variation was conducted by weighing 20 tablets individually and calculating the average weight and comparing the individual tablet weight to the average value. The following percentage deviation in weight variation is allowed.

Table No. 03: Percentage Deviation in Weight Variation.

Sr. No.	Average weight of a tablet	Percentage deviation
1	130 mg or less	10
2	130mg –324 mg	7.5
3	More than 324 mg	5

Friability Test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The % friability was then calculated by,

$$\% \text{ Friability} = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

% Friability of tablets less than 1% are considered acceptable.

% Drug Content

Two tablets was weighed and powdered. The whole amount of powdered tablet was transferred into a 100 ml volumetric flask. Add 0.1N HCl up to the mark. After few minutes the solution was filtered, rejecting first few ml of the filtrate. 10ml of filtrate was taken in a 50 ml volumetric flask and diluted up to the mark with 0.1N HCl and analyzed spectrophotometrically at 224 nm. The concentration of Telmisartan was calculated by using the standard calibration curve of Telmisartan in 0.1N HCl.

Disintegration Test

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using 0.1N HCl maintained at 37±2 0C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the 0.1N HCl maintained at 37±2 0C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

In Vitro Dissolution Study

The in vitro dissolution study of tablet was performed using USP apparatus type II (TDT- 06 PL, Electrolab, Mumbai, India) fitted with paddle (50 rpm) at 37±0.5 °C using 0.1N HCL, 900 ml as a dissolution medium. At the predetermined time intervals (10, 20, 30, 45, 75, 60, 90 and 120 minutes), 5 ml samples were withdrawn, filtered and assayed at 224 nm using a Shimadzu UV 1800 spectrophotometer (Shimadzu, Kyoto, Japan). At each time point, withdrawn volume was replaced with fresh dissolution media.

Stability Study[24]

Optimized formulation was subjected to stability study at temperature 40ºC/75 % relative humidity (RH) for a period of 1 month. The optimized formulation sealed in aluminum foil was kept at above mentioned temperature and humidity condition. At the end of studies, samples were analyzed for the in vitro drug release and % drug content and other parameters such as hardness and friability.

Comparison with Marketed Product[25]

The tablets prepared by optimized co-crystals (i.e. Telmisartan:Cinnamic Acid - 1:4) were compared with marketed tablet **Adcom T40** (from Intel Pharmaceuticals) both having 40mg

Telmisartan concentration for in vitro dissolution study. The compared result was shown table no.11.

RESULTS AND DISCUSSION

SELECTION OF CO-FACTOR

Table No.4: Solubility studies of Co-factors in Distilled Water.

Sr. No.	Ratio (mg)	Observed Solubility of Telmisartan using different co-formers							
		Batch A	Batch B	Batch C	Batch D	Batch E	Batch F	Batch G	Batch H
1	Pure Drug	0.0266	**0.0266**	**0.0266**	0.0266	0.0266	0.0266	0.0266	0.0266
2	20:80	0.0064	**0.0452**	**0.0727**	0.0062	0.0120	0.0179	0.0417	0.0126
3	40:60	0.0090	**0.0518**	**0.0664**	0.0155	0.0170	0.0252	0.0429	0.0201
4	50:50	0.0164	**0.0439**	**0.0477**	0.0203	0.0187	0.0289	0.0421	0.0337
5	60:40	0.0183	**0.0495**	**0.0575**	0.0250	0.0260	0.0259	0.0530	0.0209
6	80:20	0.0214	**0.0283**	**0.0527**	0.0363	0.0252	0.0320	0.0505	0.0235

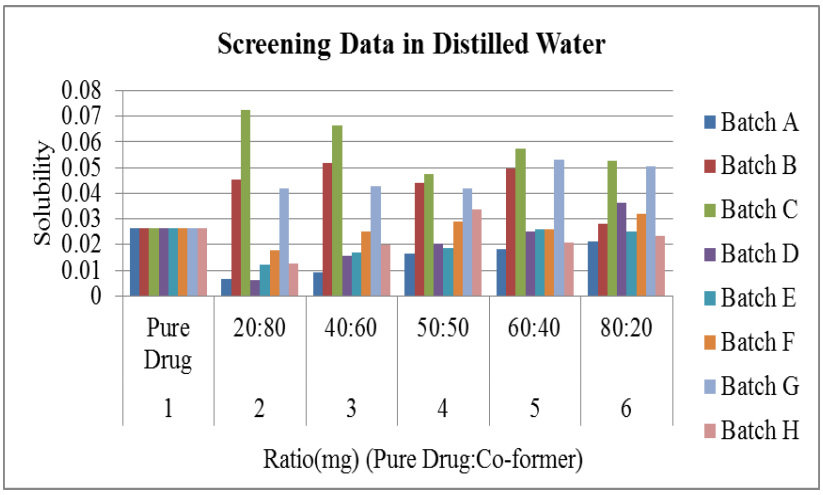

Figure 1: Screening Data in Distilled Water.

The Batch B (Telmisartan: Salicylic Acid) co-crystals and Batch C (Telmisartan: Cinnamic Acid) co-crystals shows the more solubility in Distilled Water as compare to the pure drug Telmisartan. Therefore, Salicylic Acid and Cinnamic Acid are selected as co-former for further study.

Optimization of Stoichiometric Ratio of Drug and CCF

From all methods, co-crystals prepared by Neat Grinding Method using Salicylic Acid and Cinnamic Acid as a co-crystal former and Telmisartan gave maximum solubility. Therefore, stoichiometric ratio was optimized by using this method by preparing co-crystals in different stoichiometric ratio as follows and evaluating them.

Table No. 05: Stoichiometric ratios for Batch B and C.

Sr. No.	Batch	Ratios	Sr. No.	Batch	Ratios
1	B1	1:1	11	C1	1:1
2	B2	1:2	12	C2	1:2
3	B3	1:3	13	C3	1:3
4	B4	1:4	14	C4	1:4
5	B5	1:5	15	C5	1:5
6	B6	1:10	16	C6	1:10
7	B7	1:20	17	C7	1:20
8	B8	1:30	18	C8	1:30
9	B9	1:40	19	C9	1:40
10	B10	1:50	20	C10	1:50

EVALUATION OF SELECTED CO-CRYSTALS

Solubility study

The data for solubility studies in different media are shown in Table no. 06. All co-crystals showed marked improvement in solubility in 0.1N HCL and distilled water compared to pure drug. From them, co-crystals gave maximum solubility.

Melting point

Melting points of drug, co-crystal formers and co-crystals are given in Table 06. Melting point of co-crystals were below the melting point of drug and co-crystal former and generally in between them. Altered melting points of co-crystals might be attributable to some type of interaction between drug and co former, altered packing arrangement and change in the crystallinity of molecules. Co-crystals melted as single component which indicate phase transformation and co-crystals might have formed.

Particle Size Determination

Particle size of drug was found to be 30.635 µm. There was increase in particle size of co-crystals that indicate association of drug and co-crystal former by some kind of interaction. Particle size of co-crystals was found between 50 and 75 µm. Particle sizes of co-crystals are showed in Table 6.

Table No. 6: Evaluations of Selected Co-corystals.

Batches	Ratios	Solubility± SD* (mg/ml)		Melting Points (^{o}C)	Mean Particle Sizes (µm)
		In Distilled Water	In 0.1N HCl		
Telmisartan	Pure	0.0266±0.002	0.0477±0.006	260-261	50
Salisylic Acid	Pure	0.500±0.005	4.0217±0.014	158-160	80
Cinnamic Acid	Pure	0.500±0.098	5.460±0.058	133-135	77
B1	1:1	0.0559±0.002	0.0754±0.008	194-196	70.62
B2	1:2	0.0559±0.002	0.0754±0.008	223-225	67.50
B3	1:3	0.0559±0.002	0.0754±0.008	202-204	63.75
B4	1:4	0.0559±0.002	0.0754±0.008	182-184	71.87
B5	**1:5**	**0.0559±0.002**	**0.0754±0.008**	**198-200**	**65**
B6	1:10	0.0559±0.002	0.0754±0.008	195-197	72.50
B7	1:20	0.0559±0.002	0.0754±0.008	222-224	60.62
B8	1:30	0.0559±0.002	0.0754±0.008	199-201	68.51
B9	1:40	0.0559±0.002	0.0754±0.008	183-185	69.72
B10	1:50	0.0559±0.002	0.0754±0.008	194-196	65.17
C1	1:1	0.0559±0.006	0.0778±0.008	216-218	61.88
C2	1:2	0.0559±0.006	0.0778±0.008	201-203	58.12
C3	1:3	0.0559±0.006	0.0778±0.008	190-192	56.87
C4	**1:4**	**0.0559±0.006**	**0.0778±0.008**	**195-197**	**67.24**
C5	1:5	0.0559±0.006	0.0778±0.008	217-219	56.57
C6	1:10	0.0559±0.006	0.0778±0.008	185-187	54.37
C7	1:20	0.0559±0.006	0.0778±0.008	223-225	64.38
C8	1:30	0.0559±0.006	0.0778±0.008	203-205	67.50
C9	1:40	0.0559±0.006	0.0778±0.008	196-198	65.12
C10	1:50	0.0559±0.006	0.0778±0.008	210-212	71.87

*All values are mean ± SD (n=3)

In vitro dissolution study of Final Optimize Batch of Co-crystals

Co-crystals were evaluated for *in vitro* dissolution study for selection of optimum batch. The dissolution data are shown in Table 7 and compared in Figure 2. There was a marked increase in early dissolution of drug, as well as total increase in dissolution rate of drug was observed. Batch C4 gave maximum percentage drug release (%DR) and gave drug release of 83.42% in 60 min in comparison to 13.72% from pure drug.

Table No. 7: Dissolution profile of drug and co-crystals of T:CA.

Time (Min)	Pure Drug	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
0	0	0	0	0	0	0	0	0	0	0	0
10	0	22.98	30.17	23.01	45.98	44.92	30.78	28.38	42.01	40.46	38.72
20	0	35.18	36.01	27.03	55.79	50.98	41.40	39.40	47.98	49.98	44.77
30	0.13	41.52	40.47	31.89	63.87	69.01	49.98	45.98	52.16	53.28	50.52
45	6.28	50.78	51.01	37.84	74.07	75.67	60.01	60.67	59.70	61.72	62.43
60	**13.72**	59.70	60.07	44.06	**83.42**	79.99	69.98	65.17	66.67	66.01	66.70
90	22.22	65.61	67.70	48.55	89.37	86.21	80.00	72.32	73.04	70.36	71.55
120	26.05	70.01	72.78	57.89	99.14	90.06	85.75	80.56	85.44	83.82	80.40

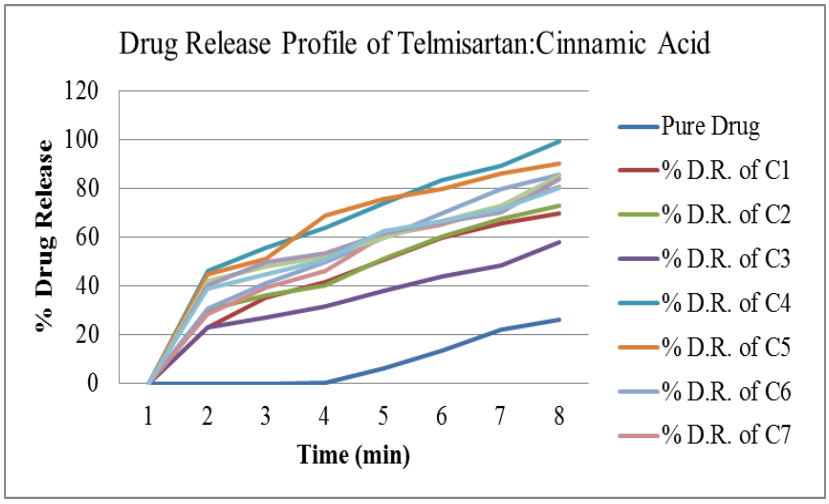

Fig 2: Comparison of dissolution profile of Telmisartan: Cinnamic Acid co-crystals.

Fourier Transform Infrared Spectroscopy

The FTIR spectra of Telmisartan (Figure 3) showed a characteristic peaks appeared at 3384.5cm^{-1} (Amine N-H Stretching), 3139.9cm^{-1} (Carboxylic acid O-H Stretching), 2902.67cm^{-1} (Alkyl C-H Stretching), 1321.15cm^{-1} (Aromatic C=C Stretching).

The FTIR spectra of Cinnamic Acid (Figure 4) showed a characteristic peaks appeared at 3139.9cm^{-1} (Carboxylic acid O-H Stretching), 2902.67cm^{-1} (Alkyl C-H Stretching), 1321.15cm^{-1} (Aromatic C=C Stretching).

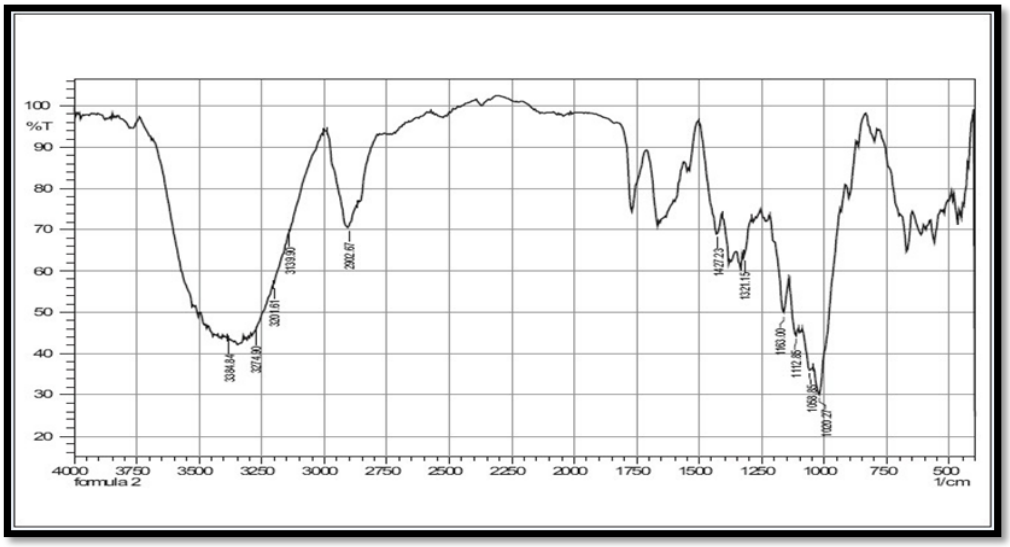

Figure 3: FTIR spectrum of Telmisartan.

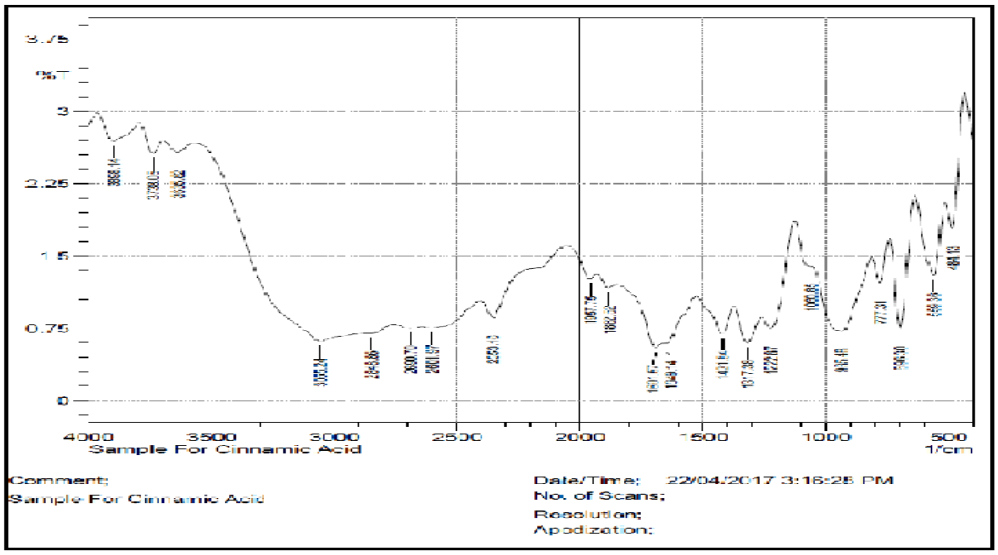

Figure 4: FTIR spectrum of Cinnamic Acid.

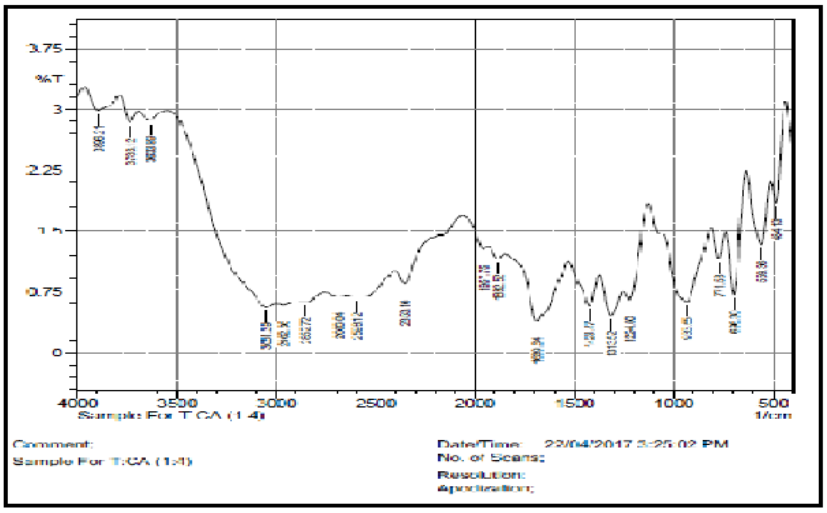

Figure 5: FTIR spectrum of optimized batch (C4) of co-crystals.

From FTIR graph of drug (Figure 3), co-former (Figure 4) and co-crystal (Figure 5), there was a shift or removal of characteristic peak of Telmisartan in case of co-crystals. This was due to formation of hydrogen bond between drug and co-crystal former. So, it was concluded that co-crystals might have formed.

Powdered X-Ray Diffraction

X-ray diffraction patterns of drug and co-crystals are shown in Figure 6 and Figure 7, respectively.

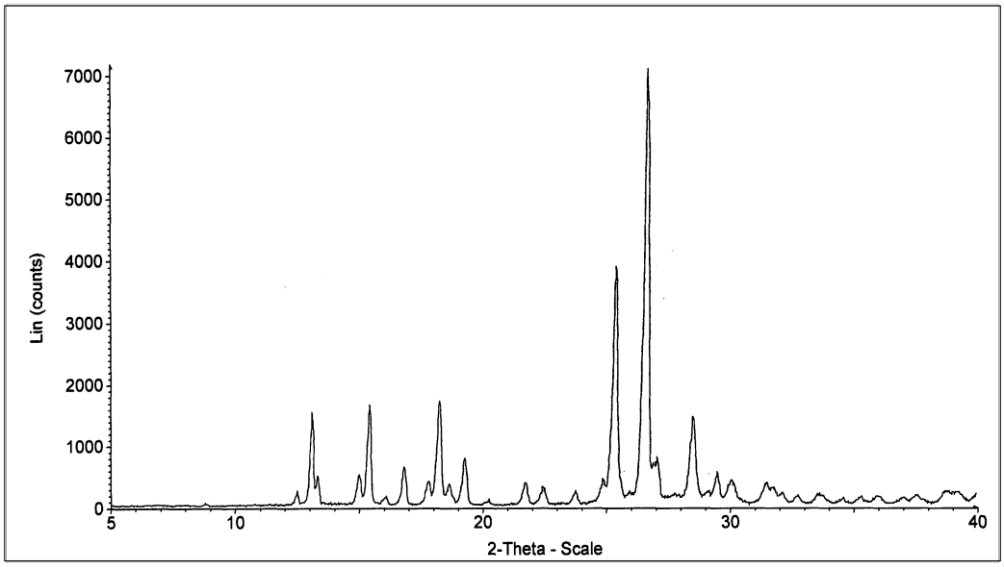

Figure 6: PXRD pattern of Telmisartan.

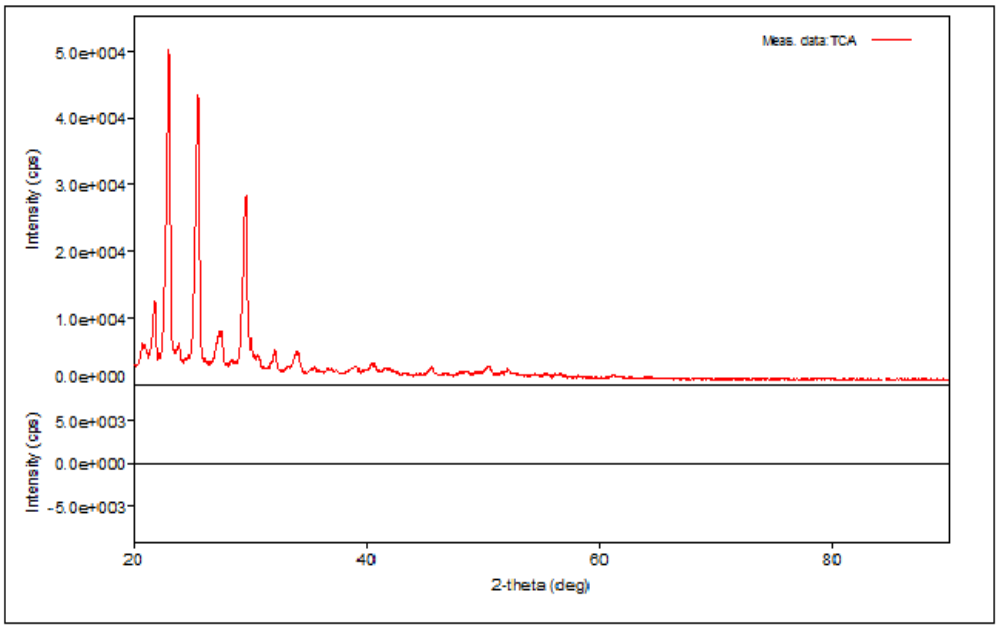

Figure 7: PXRD pattern of selected batch C4 co-crystals.

Diffraction pattern of drug and co-crystals showed that both were crystalline in nature as demonstrated by numerous distinct peaks of $2\boldsymbol{\theta}$. PXRD pattern of co-crystals showed shifting of drug peaks as well as all PXRD pattern of drug was changed in case of co-crystals. So, it was concluded that co-crystals might have formed.

EVALUATION OF TABLETS OF OPTIMIZED CO-CRYSTALS

A. Pre-Compression Evaluations

The pre-compression evaluation results are shown in table no.8. Bulk density was found to be 0.56±0.02 g/cm^3. Tapped density was found to be 0.61±0.06 g/cm^3. Carr's index was found to be 8.19±1.38%. Hausner ratio was found to be 1.089±0.03. And angle of repose was found to be 23.49±0.98^0.

Table No.8: Pre-compression Evaluation of optimized co-crystal tablets.

Sr. No.	Pre-compression Parameters	Results
1	Bulk Density (g/cm^3)*	0.56±0.02
2	Tapped Density(g/cm^3)*	0.61±0.06
3	Carr's Index (%)*	8.19±1.38
4	Hausner Ratio*	1.089±0.03
5	Angle of Repose (^{o})*	23.49±0.98

*All values are mean ± SD (n=3).

B. Post-Compression Evaluations

The post-compression evaluation results are shown in table no.9. Hardness was found to be around 3.9 kg/cm2. Weight variation was within the limit of average weight ± 10%. So, tablets were passed weight variation test. Friability was found to be 0.44±0.36. So, % friability was less than 1% which indicates tablets were passed friability test. *In vitro* disintegration time was found to be 34.34 ± 1.48 sec. Drug content was found to be around 99%.

Table 9: Post-compression evaluation of optimized co-crystal tablets.

Sr. No.	Post-compression Parameters	Results
1	Weight variation (mg)	250.12 ± 1.1
2	Hardness* (kg/cm^2)	3.9± 0.3
3	Disintegration time* (sec) (n=6)	34.34 ± 1.48
4	% friability*	0.44 ± 0.36
5	% Drug content* (n=3)	99.19 ± 0.91

*All values are mean ± SD

Stability Study of Telmisartan Co-Crystal Tablets

The result obtained after 1 month stability study at temperature 40ºC/75 % relative humidity (RH) shown in table no.10 with compared to initial results. After stability studt for 1 month, there was not much difference in results as well as in vitro dissolution from tablets (Table No.10 and Figure 8). So, the optimized formulation was stable.

Table No.10: Evaluation of optimized co-crystal tablets before and after stability study.

Sr. No.	Evaluation Parameters	Results	
		Initial	After Stability Study for 1 month
1	Weight variation (mg)	250.12 ± 1.1	250.07±0.9
2	Hardness* (kg/cm^2)	3.9± 0.3	3.82±0.2
3	Disintegration time* (sec) (n=6)	34.34 ± 1.48	36.21±1.83
4	% friability*	0.44 ± 0.36	0.52±0.18
5	% Drug content* (n=3)	99.19 ± 0.91	98.59±1.24

*All values are mean ± SD

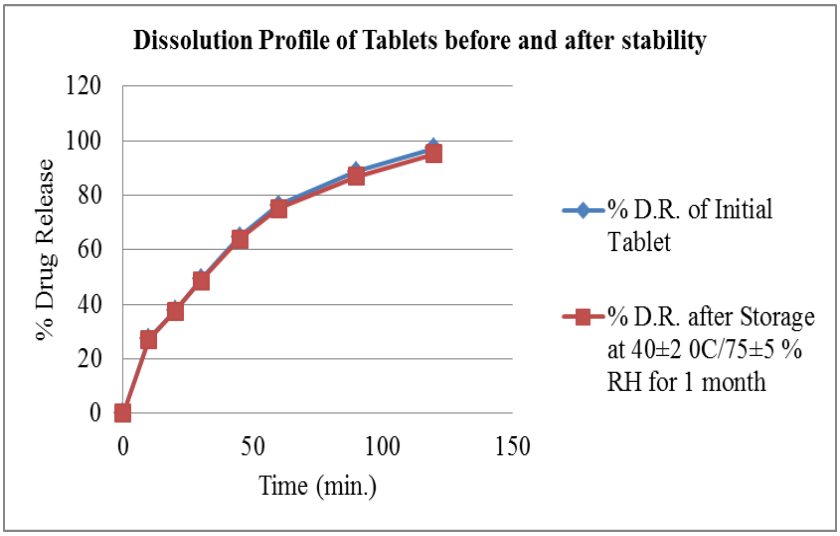

Figure No. 8: Comparison of dissolution profile of tablets before and after Stability Study.

Comparison with Marketed Product

Tablets prepared by optimized co-crystals were compared with marketed tablets for in vitro dissolution study (Table 11 and Figure 9). Percent drug release was 98.614% after 60 min, whereas for marketed product it was 70.21%. So, optimized co-crystal tablet gave better dissolution profile than marketed product **Adcom T40** (from Intel Pharmaceuticals).

Table 11: Dissolution data of optimized co-crystal tablet and marketed tablet.

Sr. No.	Time (min.)	Percentage Drug Release (% DR)*	
		Co-crystal Tablet	Marketed Tablet
1	0	0	0
2	10	27.675±1.406	19.453±0.985
3	20	37.620±1.247	26.982±1.321
4	30	49.325±1.538	39.982±1.212
5	45	64.850±1.816	53.551±1.835
6	**60**	**76.325±1.108**	**62.236±1.468**
7	90	88.725±1.321	70.206±1.784
8	120	97.275±1.472	85.406±1.675

*All values are mean ± SD (n=3)

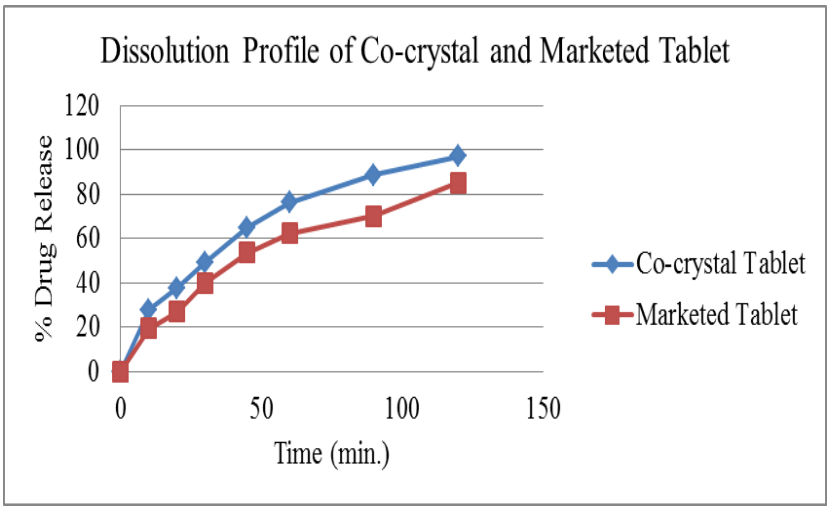

Figure 9: Comparison of dissolution profile of optimized tablets and marketed tablets.

CONCLUSION

According to biopharmaceutical classification system, Telmisartan is classified as a low solubility and high permeability drug (class II). The major problem related with Telmisartan is its low solubility and there by highly variable bioavailability after oral administration. The Tmax of Telmisartan is about 1-2 hr after oral administration. Rapid solubilization is necessary to provide rapid absorption of drug. Therefore, it is necessary to enhance the solubility and dissolution rate of Telmisartan to obtain faster onset of action, to minimize the variability in absorption and improve its overall oral bioavailability. This is achieved by formulating drug in form of co-crystals. Co-crystals prepared by grinding method and using Cinnamic Acid as a co-crystal former (1:4 stoichiometric ratio). From the above discussion it is clear that improvement in solubility and dissolution rate of Telmisartan can be achieved by co-crystals. *In vitro* dissolution of optimized Telmisartan co-crystal tablet was comparatively higher than pure drug and marketed formulation which reflect improvement in solubility.

From the study carried out it was concluded that stable co-crystals of Telmisartan with increased solubility and improved *in vitro* dissolution of Telmisartan can be successfully prepared.

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